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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.: NCT00551135

PROTOCOL NO.: A0081171

PROTOCOL TITLE: A Randomized, Double-Blind Multi-Center Dose-Ranging Study of the Efficacy and Safety of Pregabalin Compared to Placebo in the Adjunctive Treatment of Post-Surgical Pain after Primary Inguinal Hernia Repair

Study Centers: 34 centers; 1 center in Australia, 3 centers in Canada, 4 centers in India, 4 centers in Spain, 5 centers in Sweden, and 17 centers in the United States.

Study Initiation Date and Completion Dates: 18 January 2008 to 14 September 2009

Phase of Development: Phase 3

Study Objectives: The primary objective of this study was to assess the efficacy of pregabalin compared to placebo on acute pain at 24 ±4 hours following elective inguinal herniorrhaphy. The secondary objectives were to evaluate the effect of pregabalin on pain with movement following surgery, to evaluate the effect of pregabalin on pain at rest following surgery, Global Evaluation of Study Medication (GESM) effects of pregabalin, to evaluate time to first rescue medication used in the first week postoperatively, to evaluate the postoperative opioid sparing effect of pregabalin compared to placebo, to evaluate the effect of pregabalin compared to placebo on the occurrence of opioid related symptoms, to evaluate the sparing effect of pregabalin compared to placebo on the use of non opioid and any antiemetic rescue medications, to evaluate sleep interference post hospital discharge, to evaluate anxiety before surgery (BS) and after surgery, to evaluate the effect of pregabalin compared to placebo on health status, to evaluate pain severity and interference of pain on aspects of daily activities, to evaluate need for physician contacts 24 ± 4 hours and 72 ± 4 hours post discharge, to evaluate the time from end of the surgery to meet protocol specified hospital discharge criteria and Post Anesthesia Care Unit (PACU) discharge, to evaluate the influence of catastrophizing to treatment outcome, to investigate the effect of pregabalin treatment on the incidence and severity of chronic (1, 3, and 6 months) postoperative pain, to evaluate the relationship of biomarkers to treatment outcome, and to evaluate the safety and tolerability of pregabalin in the perioperative setting.

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METHODS

Study Design: This was a multicenter, multiple-dose, randomized, double-blind, 4-arm, placebo-controlled, parallel-group study involving approximately 400 subjects eligible for the efficacy analysis with pain following unilateral open mesh, Lichtenstein inguinal herniorrhaphy, with general anesthesia or Monitored Anesthesia Care (MAC).

Number of Subjects (Planned and Analyzed): A sample size of 100 per group (400 total with 600 subjects screened) was considered appropriate to provide about 90% power to detect a treatment effect of 1.0 assuming a standard deviation (SD) of 2.2.

The MITT population was applied to all parameters and was the primary analysis population. Overall, 413 of the 425 treated subjects (97.2%) were included in the MITT population, reducing to 403 subjects (94.8%) when Site 1013 was excluded. The ITT population (417 subjects, 406 subjects when Site 1013 was excluded) and PP population (307 subjects, 304 subjects when Site 1013 was excluded) were applied only to the primary and key secondary parameters. Site 1013 was excluded from the primary population, but included in the secondary sensitivity analysis population. All 425 treated subjects comprised the safety population and were analyzed for AEs, with 403 of these subjects analyzed for laboratory data.

Diagnosis and Main Criteria for Inclusion: Subjects were males aged between 18 and 75 years and who have had elective open unilateral inguinal herniorrhaphy, using mesh Lichtenstein under general anesthesia or MAC and fentanyl or sufentanil/propofol initiation and sevoflurane, isoflurane or desflurane as required for maintenance in addition to local anesthetic infiltration at the conclusion of surgery.

Study Treatment:

- Group 1 received placebo both BS and after surgery.
- Group 2 received 75 mg of pregabalin the evening BS, 75 mg of pregabalin 2 ±1 hour(s) BS, and then 150 mg/day (75 mg BID) after surgery for 1 week.
- Group 3 received 75 mg of pregabalin the evening BS, 150 mg pregabalin 2 ±1 hour(s) BS, and then 300 mg/day (150 mg BID) of pregabalin following surgery for 1 week.
- Group 4 received 25 mg of pregabalin the evening BS, 25 mg of pregabalin 2 ±1 hour(s) BS, and 50 mg (25 mg BID) after surgery for 1 week.

Taper medication was dispensed at Visit 9 (Week 1 or early termination). Taper was administered to subjects who discontinued from the study only if they had taken 4 or more days of study medication. Taper period was 1 week.

Efficacy Evaluations: The primary endpoint was the worst pain reported by subjects (Question 1 of the Modified Brief Pain Inventory-Short Form [mBPI-sf]) on the first day (approximately 24 hours) after completion of surgery. The mBPI-sf is a self-administered questionnaire developed to assess pain severity and pain interference with functional

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activities during a 24 hour period prior to evaluation. The mBPI-sf was performed at baseline (Visit 2), 24 ± 4 hours (Visit 7), 72 ± 4 hours (Visit 8) and Day 7 (Visit 9).

The key secondary efficacy endpoints were movement related pain assessment (Numeric Rating Scale [NRS]-Current Pain) during hospital and post discharge stay, average pain (mBPI-sf), and total cumulative and daily dose of opioids and tramadol used following surgery.

The other secondary efficacy endpoints were total clinically meaningful event (CME) score-opioid related symptom distress scale (OR-SDS), worst pain at 72 hours derived from mBPI-sf, pain severity index and interference index (mBPI-sf), worst pain (NRS), average pain (NRS), deep sleep interference rating scale, resting pain assessment (NRS-current pain), total and daily cumulative dose of opioids, total and daily cumulative dose of tramadol, amount of non-opioid rescue medication, cumulative and by visit CME score-OR-SDS, subject assessment of anxiety visual analog scale (VAS), Euro quality of life (EQ-5D) health questionnaire, short form 12 version acute health survey, pain catastrophizing scale, time to meet protocol defined discharge criteria on post anesthetic discharge scoring system, time to event parameters, EQ-5D health state individual item score, GESM, postoperative pain questions, work related activity scale, and neuropathic pain symptom inventory-chronic pain measure.

Safety Evaluations: Adverse events (AEs) were monitored throughout the study. The laboratory assessments were performed at screening and Week 1 (or early termination). 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 (taken 2-3 minutes after supine) and pulse rate, weight, 12-lead electrocardiogram (ECG), prospective assessment of AEs of wound healing complications up to 30 days after surgery, prior and concomitant medications and non drug treatment, and clinical contact following surgery using the post-surgery contact (PC) questionnaire that was used at the 24 ± 4 hours and 72 ± 4 hours telephone visits and at specific time points.

Statistical Methods: The primary endpoint was the worst pain reported by subjects (Question 1 of the mBPI-sf) on the first day (approximately 24 hours) after completion of surgery.

An analysis of variance (ANOVA) with model terms of treatment and study center were used to compare pregabalin and placebo groups in the primary endpoint. The baseline worst pain score (derived from mBPI-sf at baseline) or baseline Pain Catastrophizing Scale (PCS) were added to the ANOVA model if they were significant at the 0.05 level based on type III sum of squares test.

Statistical testing for the primary efficacy endpoint was done using Hochberg's adjustment for multiple comparisons to control the maximum experiment-wise type I error rate at the 0.05 level. To apply Hochberg's adjustment, comparison p-values between placebo and pregabalin 75 mg BID and 150 mg BID dose groups were first obtained independently. Then, Hochberg's adjustment kept the larger p-value (less significant) unchanged and

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adjusted the smaller p-value (more significant) to the minimum of either the larger p-value or double of the smaller nominal p-value. The pregabalin 25 mg BID group was compared with placebo only if at least 1 higher pregabalin dose group was found significantly different from placebo. This procedure was applied only to the analysis of the primary efficacy parameter.

The Modified Intent-to-Treat (MITT) population based analysis was regarded as the primary analysis. Intent-to-Treat (ITT) and Per Protocol (PP) population based analyses were regarded as secondary.

RESULTS

Subject Disposition and Demography: Subject disposition is summarized in Table 1. A total of 425 subjects received study treatment; a total of 17 subjects discontinued from the study. A total of 403 subjects were included in the primary analysis.

Table 1. Subject Disposition

	Pregabalin 50 mg	Pregabalin 150 mg	Pregabalin 300 mg	Placebo
Number (%) of subjects				
Screened 531				
Assigned to study treatment	108	106	103	108
Treated	108	106	103	108
Completed (%)	103 (95.4)	104 (98.1)	98 (95.1)	103 (95.4)
Discontinued (%)	5 (4.6)	2 (1.9)	5 (4.9)	5 (4.6)
Related to study treatment				
Adverse event	0	0	1 (1.0)	0
Not related to study treatment				
Adverse event	1 (0.9)	0	0	1 (0.9)
Lost to follow-up	0	0	0	1 (0.9)
Other	3 (2.8)	2 (1.9)	1 (1.0)	2 (1.9)
Subject no longer willing to participate in the study	1 (0.9)	0	3 (2.9)	1 (0.9)
Analyzed for Efficacy (%):				
ITT (Including Site 1013)	105 (97.2)	104 (98.1)	102 (99.0)	106 (98.1)
ITT (Excluding Site 1013)	102 (94.4)	100 (94.3)	101 (98.1)	103 (95.4)
MITT (Including Site 1013)	105 (97.2)	102 (96.2)	102 (99.0)	104 (96.3)
MITT (Excluding Site 1013)	102 (94.4)	99 (93.4)	101 (98.1)	101 (93.5)
PP (Including Site 1013)	75 (69.4)	81 (76.4)	79 (76.7)	72 (66.7)
PP (Excluding Site 1013)	74 (68.5)	79 (74.5)	79 (76.7)	72 (66.7)
Analyzed for Safety (%):				
Adverse events	108 (100.0)	106 (100.0)	103 (100.0)	108 (100.0)
Laboratory data	101 (93.5)	100 (94.3)	99 (96.1)	103 (95.4)
Safety Population	108 (100.0)	106 (100.0)	103 (100.0)	108 (100.0)

ITT = intent-to-treat; MITT = modified intent-to-treat; PP = per protocol

Acute and Follow-up Phase: Of the 425 subjects who received study treatment, 397 subjects completed the acute and the follow-up phases (subjects who reported no chronic pain at Months 1 or 3 were considered completed and were not followed-up at later visits). By the time of the follow-up phase, a total of 28 subjects had discontinued from the study, ie, an additional 11 subjects. This included 1 additional subject withdrawn due to an AE (placebo

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group, AE considered to be treatment-related (Table 1). Additionally, 8 further subjects were lost to follow-up (2, 2, 1, and 3 subjects in the pregabalin 50, 150, and 300 mg and placebo groups, respectively), and 1 further subject in the pregabalin 150 mg was withdrawn for an other reason that was not considered to be treatment-related. One additional subject in the placebo group was no longer willing to participate in the study.

Demographic characteristics were similar across treatment groups and are summarized in Table 2. The demographic characteristics with acute and follow-up combined were the same as those detailed in Table 2.

Table 2. Demographic Characteristics

	Pregabalin 50 mg (N=108)	Pregabalin 150 mg (N=106)	Pregabalin 300 mg (N=103)	Placebo (N=108)
Age, years				
Mean (SD)	48.4 (13.7)	48.8 (13.6)	48.4 (13.8)	47.2 (14.5)
Range	18-75	19-73	18-71	18-74
Race, number (%) of subjects				
White	82 (75.9)	89 (84.0)	85 (82.5)	84 (77.8)
Black	6 (5.6)	2 (1.9)	6 (5.8)	6 (5.6)
Asian	13 (12.0)	7 (6.6)	9 (8.7)	13 (12.0)
Other	7 (6.5)	8 (7.5)	3 (2.9)	5 (4.6)
Ethnicity, number (%) of subjects				
Hispanic/Latino	23 (21.3)	26 (24.5)	23 (22.3)	27 (25.0)
Not Hispanic/Latino	85 (78.7)	80 (75.5)	80 (77.7)	81 (75.0)
Weight (kg)				
Mean (SD)	79.1 (14.3)	81.6 (15.0)	78.9 (12.3)	80.1 (14.1)
Range	48.0-127.9	41.0-121.5	48.0-108.8	48.0-124.7
Height (cm)				
Mean (SD)	175.0 (7.5)	175.6 (7.6)	174.6 (7.5)	175.6 (7.5)
Range	153.0-193.0	160.0-195.0	157.0-191.0	152.0-191.0
Body Mass Index (kg/m^2)				
Mean (SD)	25.7 (4.0)	26.4 (4.0)	25.8 (3.4)	25.9 (3.7)
Range	16.8-42.7	16.0-39.4	18.0-34.9	18.3-35.3
Primary Diagnosis MedDRA (v12.0) Preferred term				
Inguinal hernia	108	106	103	108
Duration Since First Diagnosis (years)[a]				
Mean	1.0	1.4	1.2	1.4
Range	0.0-12.2	0.0-21.0	0.0-21.1	0.0-21.2
Unspecified (N)	1	0	0	1

MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects; SD = standard deviation
[a]Duration from first diagnosis to Day 1 of study

Efficacy Results: Table 3 summarizes the worst pain (mBPI-sf) at 24 hours PS in the MITT population (excluding Site 1013 due to multiple Good Clinical Practice violations). There were no significant differences in the mean baseline value of worst pain for any dose of pregabalin compared to placebo. The efficacy of pregabalin 300 mg compared to placebo on acute worst pain at 24 ±4 hours following elective inguinal herniorrhaphy showed a significant difference from placebo before multiple comparisons adjustment. The results were not significant after the multiple comparisons adjustment was done. The LS means difference between pregabalin 300 mg and placebo at 24 hours PS was -0.7 (standard error

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[SE] = 0.33) with a Hochberg adjusted p-value of 0.0668, 95% CI (un-adjusted) of (-1.4, -0.1), and nominal p-value of 0.0334. There was no significant treatment difference for the pregabalin 50 and 150 mg doses compared to placebo. The results of the sensitivity analyses with MITT (including Site 1013) and ITT (excluding and including Site 1013) populations were similar. However, the worst pain (mBPI-sf) at 24 hours PS in the PP (excluding and including Site 1013) population was not significantly different to placebo for any dose of pregabalin.

Table 3. Worst Pain (mBPI-sf) at Baseline and 24 Hours (Excluding Site 1013) - MITT Population

	Pregabalin 50 mg	Pregabalin 150 mg	Pregabalin 300 mg	Placebo
Baseline[a]				
n	102	99	101	101
Mean (SD)	2.0 (2.15)	1.7 (2.01)	1.9 (2.08)	2.2 (2.50)
LS Mean (SE)	2.0 (0.22)	1.7 (0.23)	1.9 (0.22)	2.2 (0.22)
Difference from Placebo (SE)	-0.2 (0.30)	-0.5 (0.30)	-0.3 (0.30)	-
95% CI	(-0.8, 0.4)	(-1.1, 0.1)	(-0.9, 0.3)	-
p-value	0.5385	0.1045	0.3570	-
24 Hours PS				
n	102	99	101	101
Mean (SD)	5.4 (2.47)	5.7 (2.25)	4.9 (2.80)	5.6 (2.46)
LS Mean (SE)	5.2 (0.24)	5.4 (0.25)	4.7 (0.24)	5.4 (0.24)
Difference from Placebo (SE)	-0.1 (0.33)	0.1 (0.33)	-0.7 (0.33)	-
95% CI	(-0.8, 0.5)	(-0.6, 0.7)	(-1.4, -0.1)	-
p-value	0.6932	0.8003	0.0334	-
Adjusted p-value[b]	-	0.8003	0.0668	-

n = number of subjects that were analyzed at the given visit; CI = confidence interval; SD = standard deviation; SE = standard error; LS = least square mean; mBPI-sf = Modified Brief Pain Inventory; MITT = Modified Intent-to-Treat Population; PS = Post Surgery
LS Means from ANOVA model with terms of treatment, pooled center and baseline worst pain (for baseline visit ANOVA model with terms of treatment and pooled center). Centers with less than 8 treated subjects were combined into pooled centers. The pregabalin 50 mg group was compared with placebo only if at least 1 higher pregabalin dose group was found significantly different from placebo after the Hochberg's adjustment.
[a] Baseline was collected at various visit windows and was hernia-related pain prior to surgery (ie, not post-surgical pain).
[b] p-value was adjusted using the Hochberg's procedure.

Key Secondary Efficacy Results

Significant differences from placebo were observed 2 hours BS following pregabalin 150 mg (-0.3, SE = 0.14, p-value = 0.0197) and 1 hour PS following pregabalin 300 mg group (-1.0, SE = 0.32, p-value = 0.0018) in the pain (NRS) caused by sitting for the MITT population. No significant differences compared to placebo were observed in pain (NRS) caused by sitting for any of the pregabalin dose levels at 2 hours PS, 3 hours PS, Day 2 PS, or for AUC_{1-48}. The sensitivity analysis results (including Site 1013) were similar for the pain (NRS) and pain (AUC_{1-48}) (NRS) caused by sitting. Similar results were also obtained for the pain (NRS) and pain (AUC_{1-48}) (NRS) caused by sitting for the ITT and PP populations.

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Significant difference from placebo was observed 1 hour PS following pregabalin 300 mg group (-0.8, SE = 0.38, p-value = 0.0348) in the pain (NRS) caused by walking for the MITT population. No significant differences compared to placebo were observed in the pain (NRS) caused by walking for any of the pregabalin dose levels at 2 hours BS, 2 hours PS, 3 hours PS, Day 2 PS, or for AUC_{1-48}. The sensitivity analysis results (including Site 1013) were similar for the pain (NRS) and pain (AUC_{1-48}) (NRS) caused by walking. Similar results were also obtained for the pain (NRS) and pain (AUC_{1-48}) (NRS) caused by walking for the ITT population. However, there were no statistically significant difference from placebo for the pain (NRS) and pain (AUC_{1-48}) (NRS) caused by walking for the PP population.

Movement pain (NRS), in particular pain caused by coughing was the most sensitive measure and was more sensitive than other movement pain (walking and sitting induced pain). The results of the pain (NRS) caused by coughing were consistent with the primary endpoint, worst pain at 24 hours for pregabalin 300 mg, in terms of the effect size on Day 2 PS (ie, a significant difference from placebo was observed in pain (NRS) caused by coughing on the same day as primary endpoint for the pregabalin 300 mg group [-0.7, SE = 0.35, p-value = 0.0325]). Significant difference from placebo was also observed 1 hour PS following pregabalin 300 mg group (-0.9, SE = 0.35, p-value = 0.0104). No significant differences compared to placebo were observed for any of the pregabalin dose levels at 2 hours BS, 2 hours PS, 3 hours PS, or for AUC_{1-48}. The sensitivity analysis results (including Site 1013) were similar for the pain (NRS) and pain (AUC_{1-48}) (NRS) caused by coughing. The results of the pain (NRS) and pain (AUC_{1-48}) (NRS) caused by coughing for the ITT population were similar to the results obtained with the MITT population. There were no statistically significant difference from placebo for the pain (NRS) and pain (AUC_{1-48}) (NRS) caused by coughing for the PP population.

No significant difference from placebo was observed in any of the treatment groups in the average pain (mBPI-sf) at 24 and 72 hours PS for the MITT population. Similar results were also obtained for the average pain (mBPI-sf) at scheduled visits for the ITT and PP populations.

The cumulative doses of opioids were calculated in oral morphine equivalents (mg) and the cumulative doses of tramadol were calculated in original units. A significant difference from placebo was observed in the total cumulative dose of opioids (including tramadol) following 300 mg at all scheduled time points until Day 7, pregabalin 150 mg at 24 hours PS, and pregabalin 50 mg on Days 6 and 7 PS. The statistical significance observed on Days 2-7 PS between pregabalin 300 mg and placebo group was primarily contributed by the residual effect of the 24 hour PS difference, which was supported by the results of the daily cumulative dosing. The use of opioids (including tramadol) was consistent with the results of the primary endpoint for the pregabalin 300 mg dose; an opioid sparing effect was observed with pregabalin 300 mg compared to placebo with a 59% reduction (p-value = 0.0024) in the use of opioids (including tramadol) at 24 hours PS. The use of opioids at 24 hours PS was reduced by 41% (p-value = 0.0347) and 36% (p-value = 0.0630) with pregabalin 150 mg and 50 mg, respectively compared to placebo. The cumulative dose was generally lower in the pregabalin higher dose group when compared with the lower dose group or placebo for the treatment period. The sensitivity analysis results (including Site 1013) were similar for the total cumulative dose of opioids (including tramadol) used

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after surgery at scheduled visits. Similar results were obtained for the total cumulative dose of opioids (including tramadol) for the ITT population except for pregabalin 50 mg on Day 6 including Site 1013. However, there was no statistically significant difference from placebo for the total cumulative dose of opioids (including tramadol) used after surgery for the PP population.

The daily cumulative and total cumulative doses of opioids (including tramadol) were identical at 24 hours PS, as expected. The results at later days were not significant for pregabalin dose groups compared to placebo for the MITT population. The sensitivity analysis results (including Site 1013) were similar for the daily cumulative dose of opioids (including tramadol) used after surgery at scheduled visits. Similar results were obtained for the daily cumulative dose of opioids (including tramadol) for the ITT population. However, there was no statistically significant difference from placebo for the daily cumulative dose of opioids (including tramadol) used after surgery for the PP population.

Other Secondary Efficacy Results

No significant difference from placebo was observed in any treatment group for worst pain (mBPI-sf) at 72 hours in the MITT population.

A significant difference from placebo was observed in the worst pain (NRS) following pregabalin 300 mg at 1 hour PS, 2 hours PS, 3 hours PS, and Day 1 PS for the MITT population. The results at 1 hour PS, 2 hours PS, 3 hours PS and Day 1 PS were quite consistent with the coughing pain results and confirmed the primary endpoint.

Significant difference from placebo was observed in the current pain (NRS) at rest following pregabalin 300 mg at 1 hour PS (-1.0, SE = 0.27, p-value = 0.0004) and end of treatment on Day 9 PS (-0.8, SE = 0.27, p-value = 0.0029), and pregabalin 50 mg group at 1 hour PS (-0.6, SE = 0.27, p-value = 0.0401) and end of treatment on Day 9 PS (-1.1, SE = 0.28, p-value = 0.0002).

A significant difference from placebo was observed in the pain interference index score (mBPI-sf) following pregabalin 50 mg, 150 mg and 300 mg at 24 hours PS for the MITT population. No significant difference from placebo was observed in the pain severity index score (mBPI-sf) in the MITT population.

A significant difference from placebo was observed in the average pain (NRS) following pregabalin 300 mg at 1 hour PS (-0.7, SE = 0.26, p-value = 0.0111) for the MITT population.

A significant difference from placebo was observed in the sleep interference following pregabalin 300 mg at Day 2 PS, Day 3 PS and Day 9 PS and pregabalin 50 mg at Day 9 PS for the MITT population.

Significant difference from placebo was also observed in the total cumulative dose of opioids alone used after surgery following pregabalin 300 mg at all scheduled visits (24 hours PS, 48 hours PS, 72 hours PS, Day 4 PS, Day 5 PS, Day 6 PS and Day 7 PS), pregabalin 150 mg at 24 hours PS, and pregabalin 50 mg at 24 hours PS, Day 4 PS, Day 5 PS, Day 6 PS and Day 7 PS. The statistical significance observed after Day 1 PS between pregabalin 300 mg

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and placebo group, and pregabalin 50 mg and placebo group was primarily contributed by the residual effect of the 24 hour PS difference, which was supported by the results of the daily cumulative dosing. No significant difference from placebo was observed in the total and daily cumulative dose of tramadol (mg) alone used after surgery at the scheduled visits for the MITT population.

The incidence of CME was relatively lower due to the limited use of opioids during the study. Therefore, no significant difference from placebo was observed in the total CME score (OR-SDS) at scheduled visits for the MITT population.

Significant difference from placebo was observed in the VAS anxiety score following pregabalin 150 mg at Day 2 PS, Day 3 PS and Day 4 PS.

There was no significant effect of pregabalin compared to placebo on health status.

Subjects on pregabalin 300 mg, 150 mg and 50 mg reported lower catastrophizing total score compared to placebo at 3 hours PS. The catastrophizing total score was slightly lower for pregabalin 300 mg compared to pregabalin 150 mg and 50 mg at 3 hours PS. There was no significant difference from placebo in the PCS total score change from baseline to 3 hours PS and end of treatment for the MITT population. There was a significant difference from placebo in the subscale of helplessness change from baseline at 3 hours PS for the MITT population following pregabalin 50 mg (-1.0, SE = 0.50, p-value = 0.0430).

Based on the log-rank test, there were no significant differences between pregabalin groups and placebo for the time to event parameters.

Significant difference from placebo was observed in the GESM following pregabalin 300 mg at 24 hours PS ($p = 0.0021$) and at the end of treatment ($p = 0.0012$). There were more subjects in the pregabalin 300 mg treatment group who rated the medication as excellent compared to pregabalin 150 mg and 50 mg at 24 hours PS and end of treatment.

There was no significant difference from placebo in the categorical response from PC Questions at 24 and 72 hours PS in the MITT population.

There was no significant difference from placebo in the chronic post-operative pain at 1, 3 and 6 months PS for the MITT population.

Safety Results: There were no deaths reported in the study. Seven subjects experienced treatment-emergent serious adverse events (SAEs), of which 2 were treatment-related (Table 4).

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Table 4. Serious Adverse Events

Subject (sex/age [years])	Preferred term[a]	Action taken (drug level)	Therapy Stop Day	Event Onset Day	Outcome	Sponsor/ Investigator Causality
Pregabalin 50 mg						
10361021 (M/63)	Muscular Weakness	Dose Not Changed	9	2	Resolved	Unrelated/Unrelated
10711007 (M/68)	Gastric Ulcer Hemorrhage	Post-Therapy	9	9	Resolved	Unrelated/Unrelated
10791049 (M/57)	Guillain-Barre Syndrome	Post-Therapy	8	24	Unknown	Unrelated/Related
Pregabalin 150 mg						
10931030 (M/51)	Amnesia	Dose Not Changed	10	12	Not Recovered	Related/Related
Placebo						
10131012 (M/63)	Hematoma	Post-Therapy	4	14	Resolved	Unrelated/Unrelated
10181006 (M/48)	Vomiting	Dose Not Changed	N/A	2	Resolved	Unrelated/Unrelated
10361008 (M/47)	Abdominal Pain	Dose Not Changed	7	5	Resolved	Unrelated/Unrelated
	Pyrexia	Dose Not Changed	7	5	Resolved	Unrelated/Unrelated

M = male, F = Female, [a]MedDRA = Medical Dictionary for Regulatory Activities v12.0

Four subjects permanently discontinued due to AEs, of which 2 were treatment-related (Table 5).

Table 5. Discontinuations due to Treatment-Emergent Adverse Events

Sex/Age (years)	Preferred term[a]	Start day[b]	Stop day[b]	Severity	Outcome	Causality	SAE
Pregabalin 50 mg							
M/48	Pruritus	2	5	Moderate	Resolved	Other (Unknown etiology)	No
Pregabalin 300 mg							
M/69	Dizziness	2	9	Mild	Resolved	Study drug	No
Placebo							
M/63	Hematoma	14	15	Moderate	Resolved	Other (Wound complication)	Yes

MedDRA = Medical Dictionary for Regulatory Activities, M = male
[a]MedDRA v12.0, [b]Day relative to start of study treatment
One subject (Placebo) permanently discontinued in adverse event data but discontinued during the follow-up phase. This subject is not reported. Only discontinuations that occurred during acute phase are summarized in this report.

Two subjects had the study drug temporarily stopped due to an AE (Table 6).

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Table 6. Temporary Discontinuations or Dose Reductions due to Treatment-Emergent Adverse Events

Sex/Age [years]	Preferred term[a]	Start day[b]	Stop day[b]	Severity	Outcome	Causality	Study Drug Action	SAE
Pregabalin 300 mg								
M/29	Rash	8	17	Mild	Resolved	Other (Unknown)	Stopped temporarily	No
Placebo								
M/47	Nausea	5	37	Mild	Resolved	Disease under study	Stopped temporarily	No

MedDRA = Medical Dictionary for Regulatory Activities, M = male, SAE = serious adverse event
[a]MedDRA v12.0
[b]Day relative to start of study treatment

Treatment-emergent AEs are summarized in Table 7. A total of 224 subjects experienced a total of 794 AEs, of which 351 were treatment-related.

Table 7. Summary of Treatment-Emergent (All Causality) Adverse Events

	Pregabalin 50 mg (N=108)	Pregabalin 150 mg (N=106)	Pregabalin 300 mg (N=103)	Placebo (N=108)
Number (%) of subjects:				
Subjects evaluable for adverse events	108	106	103	108
Number of adverse events	194	184	202	214
Subjects with adverse events	56 (51.9)	53 (50.0)	61 (59.2)	54 (50.0)
Subjects with serious adverse events	3 (2.8)	1 (0.9)	0	3 (2.8)
Subjects with severe adverse events	5 (4.6)	2 (1.9)	7 (6.8)	3 (2.8)
Subjects who discontinued due to adverse events	1 (0.9)	0	1 (1.0)	2 (1.9)
Subjects with dose reductions or who temporarily discontinued due to an adverse event	0	0	1 (1.0)	1 (0.9)

N=total number of subjects

Acute and Follow-up Phase: The results with acute and follow-up combined were similar to those mentioned in Table 7 except for an increase in the number of treatment-emergent AEs from 184 to 185 following pregabalin 150 mg. The treatment-related AEs with acute and follow-up combined were similar to those of the acute phase tables.

The incidence of treatment-emergent AEs (in ≥2% subjects in any treatment group) is summarized by MedDRA (v12.0) preferred term and by body system in Table 8. The most frequently reported AE was somnolence (102 subjects; 24, 25, 25, and 28 subjects in pregabalin 50 mg, 150 mg, 300 mg and placebo groups, respectively) followed by constipation (97 subjects; 21, 22, 27, and 27 subjects in pregabalin 50 mg, 150 mg, 300 mg and placebo groups, respectively), fatigue (88 subjects; 24, 18, 23, and 23 subjects in pregabalin 50 mg, 150 mg, 300 mg and placebo groups, respectively) and dizziness (80 subjects; 15, 20, 29, and 16 subjects in pregabalin 50 mg, 150 mg, 300 mg and placebo groups, respectively). Most incidences of somnolence, constipation, fatigue and dizziness were mild or moderate in severity. The incidence of some spontaneous AEs (eg, nausea,

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vomiting), typically associated with opioids, was generally low in the pregabalin 300 mg treatment group. Most of the other AEs were mild to moderate in severity; severe AEs included gastrointestinal disorders, general disorders and administration site conditions, nervous system disorders, renal and urinary disorders, and vascular disorders.

Table 8. Incidence of Treatment-Emergent (All Causality) Adverse Events in ≥2% Subjects in Any Treatment Group

Body System Class and MedDRA Preferred Term (v12.0) n (%)	Pregabalin 50 mg (N=108)	Pregabalin 150 mg (N=106)	Pregabalin 300 mg (N=103)	Placebo (N=108)
Nervous System Disorders				
Somnolence	24 (22.2)	25 (23.6)	25 (24.3)	28 (25.9)
Dizziness	15 (13.9)	20 (18.9)	29 (28.2)	16 (14.8)
Disturbance in attention	11 (10.2)	11 (10.4)	15 (14.6)	16 (14.8)
Headache	5 (4.6)	3 (2.8)	1 (1.0)	3 (2.8)
Gastrointestinal Disorders				
Constipation	21 (19.4)	22 (20.8)	27 (26.2)	27 (25.0)
Nausea	21 (19.4)	18 (17.0)	14 (13.6)	22 (20.4)
Vomiting	2 (1.9)	7 (6.6)	1 (1.0)	7 (6.5)
General Disorders And Administration Site Conditions				
Fatigue	24 (22.2)	18 (17.0)	23 (22.3)	23 (21.3)
Pyrexia	1 (0.9)	0	1 (1.0)	4 (3.7)
Pain	1 (0.9)	0	3 (2.9)	1 (0.9)
Renal and Urinary Disorders				
Dysuria	10 (9.3)	6 (5.7)	10 (9.7)	10 (9.3)
Urinary retention	1 (0.9)	3 (2.8)	2 (1.9)	2 (1.9)
Skin and Subcutaneous Tissue Disorders				
Pruritus	9 (8.3)	7 (6.6)	4 (3.9)	6 (5.6)
Psychiatric Disorders				
Confusional state	6 (5.6)	3 (2.8)	8 (7.8)	6 (5.6)
Insomnia	1 (0.9)	0	3 (2.9)	3 (2.8)
Vascular Disorders				
Hypotension	7 (6.5)	3 (2.8)	4 (3.9)	2 (1.9)
Injury, Poisoning and Procedural Complications				
Incision site pruritus	0	1 (0.9)	4 (3.9)	3 (2.8)
Cardiac Disorders				
Bradycardia	3 (2.8)	0	0	1 (0.9)

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, 2 additional AEs were reported with acute and follow-up combined.

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 (0.9%) subject in the pregabalin 50 mg group had a past medical history of myocardial infarction (questionable old septal myocardial infarction predose) that was considered

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clinically significant; and 1 (1.0%) subject in the pregabalin 300 mg group had abnormal ECG findings (sinus rhythm with marked sinus arrhythmia, minimal voltage criteria for LVH [possibly normal variant], non-specific t wave abnormality, prolonged QT) that were considered clinically significant. Subjects' weight was not markedly changed at the end of treatment compared to baseline. Supine temperature was not changed at the end of treatment for any subject in any treatment group. The majority (>95%) of subjects had no surgical wound healing complications.

Summary of Results

- The efficacy of pregabalin 300 mg compared to placebo on acute worst pain at 24 ±4 hours following elective inguinal herniorrhaphy showed a significant difference from placebo before multiple comparisons adjustment. The results were not significant after the multiple comparisons adjustment was done. The LS means difference between pregabalin 300 mg and placebo at 24 hours PS was -0.7 (SE = 0.33) with a Hochberg adjusted p-value of 0.0668, 95% CI (un-adjusted) of (-1.4, -0.1), and nominal p-value of 0.0334. Efficacy was not observed for the pregabalin 150 mg and 50 mg groups for the primary endpoint.

- Movement pain (NRS), in particular pain caused by coughing was the most sensitive measure and was more sensitive than other movement pain (walking and sitting induced pain). The results of the pain (NRS) caused by coughing were consistent with the primary endpoint, worst pain at 24 hours for pregabalin 300 mg, in terms of the effect size on Day 2 PS (ie, a significant difference from placebo was observed in pain (NRS) caused by coughing on the same day as primary endpoint for the pregabalin 300 mg group). Significant difference from placebo was also observed in pain (NRS) caused by sitting, walking and coughing for the MITT population 1 hour PS following pregabalin 300 mg group.

- The cumulative doses of opioids were calculated in oral morphine equivalents (mg). A significant difference from placebo was observed in the total cumulative dose of opioids (including tramadol) following pregabalin 300 mg at all scheduled time points until Day 7, pregabalin 150 mg at 24 hours PS, and pregabalin 50 mg on Days 6 and 7 PS. The use of opioids (including tramadol) was consistent with the results of the primary endpoint for the pregabalin 300 mg dose; an opioid sparing effect was observed with pregabalin 300 mg compared to placebo with a 59% reduction (p-value = 0.0024) in the use of opioids (including tramadol) at 24 hours PS. The use of opioids at 24 hours PS was reduced by 41% (p-value = 0.0347) and 36% (p-value = 0.0630) with pregabalin 150 mg and 50 mg, respectively compared to placebo. The cumulative dose was generally lower in the pregabalin higher dose group when compared with the lower dose group or placebo for the treatment period. Significant difference from placebo was also observed in the total cumulative dose of opioids alone (excluding tramadol) used after surgery following pregabalin 300 mg at all scheduled visits (24 hours PS, 48 hours PS, 72 hours PS, Day 4 PS, Day 5 PS, Day 6 PS and Day 7 PS), pregabalin 150 mg at 24 hours PS, and pregabalin 50 mg at 24 hours PS, Day 4 PS, Day 5 PS, Day 6 PS and Day 7 PS.

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- No significant difference from placebo was observed in any of the treatment groups in the average pain (mBPI-sf) for the MITT population at 24 and 72 hours PS.

- The primary endpoint of worst pain, though just missed statistical significance for pregabalin 300 mg at 24 hours on Day 2, was positive the night before from NRS worst pain (on Day 1 PS) with a slightly larger difference of 0.8 (p-value = 0.0157). A significant difference from placebo was also observed in the NRS worst pain following pregabalin 300 mg at 1 hour PS, 2 hours PS, and 3 hours PS for the MITT population.

- Significant difference from placebo was observed in the current pain (NRS) at rest following pregabalin 300 mg at 1 hour PS (-1.0, SE = 0.27, p-value = 0.0004).

- Significant difference from placebo was observed in the GESM following pregabalin 300 mg at 24 hours PS (p = 0.0021) and at the end of treatment (p = 0.0012). There were more subjects in the pregabalin 300 mg treatment group who rated the medication as excellent compared to pregabalin 150 mg and 50 mg at 24 hours PS and end of treatment.

- A significant difference from placebo was observed in the pain interference index score (mBPI-sf) following pregabalin 50 mg, 150 mg and 300 mg at 24 hours PS for the MITT population. No significant difference from placebo was observed in the pain severity index score (mBPI-sf) in the MITT population.

- A significant difference from placebo was observed in the sleep interference following pregabalin 300 mg at Day 2 PS and Day 3 PS for the MITT population.

- Significant difference from placebo was observed in the VAS anxiety score following pregabalin 150 mg at Day 2 PS, Day 3 PS and Day 4 PS.

- The incidence of CME was low due to the limited use of opioids during the study. Therefore, no significant difference from placebo was observed in the total CME score (OR-SDS) at scheduled visits for the MITT population.

- There was no significant effect of pregabalin compared to placebo on health status.

- There was no significant difference from placebo in the categorical response from PC Questions at 24 and 72 hours PS in the MITT population.

- Subjects on pregabalin 300 mg, 150 mg and 50 mg reported lower catastrophizing total score compared to placebo at 3 hours PS. The catastrophizing total score was slightly lower for pregabalin 300 mg compared to pregabalin 150 mg and 50 mg at 3 hours PS. There was no significant difference from placebo in the PCS total score change from baseline to 3 hours PS and end of treatment for the MITT population.

- Based on the log-rank test, there were no significant differences between pregabalin groups and placebo for the time to event parameters.

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- There was no significant difference from placebo in the chronic post-operative pain at 1, 3 and 6 months PS for the MITT population.

- There were no deaths reported in the study. Seven subjects experienced SAEs and 224 subjects experienced a total of 794 AEs, of which 351 were treatment-related. The number of treatment-emergent, all causality AEs was similar across the pregabalin dosing groups (184-202 AEs per group) with slightly more occurring in the placebo group (214 AEs). Approximately 50%-52% of subjects experienced treatment-emergent AEs in the pregabalin 50 and 150 mg groups and the placebo group; this figure was higher (59% in the pregabalin 300 mg group. Overall, the pregabalin 150 mg group had the lowest number of all causality AEs (184) and treatment-related AEs (71). The most frequently reported AE was somnolence (102 subjects) followed by constipation (97 subjects), fatigue (88 subjects) and dizziness (80 subjects). The incidence of some spontaneous AEs (ie, nausea, vomiting), typically associated with opioids, was low in the pregabalin 300 mg treatment group.

CONCLUSIONS:

- None of the pregabalin dose groups were significantly different from placebo in the primary endpoint, worst pain at 24 hours after surgery, when analyzed in accordance with the protocol-specified procedure, including adjustment for multiple comparisons. Pregabalin 300 mg significantly reduced worst pain at 24 hours, the primary efficacy endpoint, before multiple comparisons adjustment. Efficacy was not observed with the pregabalin 150 mg or 50 mg groups for the primary efficacy endpoint.

- Statistically significant results were noted with pregabalin 300 mg for a number of secondary efficacy related assessments at varying assessment time points, for example, movement pain (NRS), reduction in cumulative dose of opioid used, current pain (NRS) at rest, GESM, pain interference index score, and sleep interference. In addition, worst pain (NRS) separated from placebo for the pregabalin 300 mg dose group but not for the pregabalin 150 or 50 mg dose groups on Day 1 following surgery ($p = 0.0157$).

- Overall, the results of this study provide evidence of efficacy with pregabalin at a dose of 300 mg in elective inguinal herniorrhaphy. Pregabalin 300, 150 and 50 mg administered for 2 doses prior to inguinal hernia surgery and for up to 1 week following surgery was 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.

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