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

PROTOCOL NO.: A0081107

PROTOCOL TITLE: A 17-Week, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multi-Center Trial of Pregabalin for the Treatment of Chronic Central Neuropathic Pain After Spinal Cord Injury

Study Centers: A total of 60 centers (1 center in Chile, 3 centers in China, 1 center in Colombia, 3 centers in the Czech Republic, 1 center in Hong Kong, 6 centers in India, 22 centers in Japan, 3 centers in the Philippines, 2 centers in the Russian Federation, and 18 centers in the United States [US]) enrolled subjects.

Study Initiation and Final Completion Dates: 23 January 2007 to 28 February 2011

Phase of Development: Phase 3

Study Objectives:

Primary:

- To evaluate the efficacy of pregabalin compared with placebo for the treatment of chronic central neuropathic pain after spinal cord injury (SCI).

Secondary:

- To evaluate the safety and tolerability of pregabalin in the treatment of chronic central neuropathic pain after SCI.
- To evaluate the effect of pregabalin on the following items in subjects with chronic central neuropathic pain after SCI:
    a. Pain-related sleep interference and overall sleep disturbance;
    b. Self-reported symptoms of depression and anxiety;
    c. Subject global impressions of change and quality-of-life;
    d. Functional limitations due to pain interference;
    e. Neuropathic pain symptoms;

f. Quantitative assessment of neuropathic pain.

METHODS

Study Design: This was a randomized, double-blind, placebo-controlled, 2-arm, multicenter study in subjects with SCI. Following Screening (Visit 1), subjects who met inclusion criteria and none of the exclusion criteria were randomized to study treatment at Visit 2 and entered a 4-week dose-adjustment phase (through Visit 4), which was followed by a 12-week dose maintenance phase (through Visit 7). At the end of 16 weeks of treatment there was a 1-week taper phase; after treatment there was a final follow-up visit (Visit 8). The duration of this study was 17 weeks. The schedule of activities is presented in Table 1.

Table 1. Schedule of Activities

Study Period	**Screening**	**Double Blind Treatment Phase**						**Follow-Up**
	V1 to V2: Up to 2 Weeks	**V2 to V4: 4-Week Dose Adjustment**		**V4 to V7: 12-Week Maintenance**			**V7 to 1 Week After V7: 1-Week Taper**	**1-Week Off-Treatment**
Clinic Visit	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**
	Screening	**Randomization**					**Termination**[a]	**Follow-Up**[a]
Week in Study	**-2**	**0**	**2**	**4**	**8**	**12**	**16**	**18**
Study Day[b]	**-14**	**1**	**15**	**29**	**57**	**85**	**113**	**127**
Telephone contact		X[c]	X[c]	X[d]	X[d]	X[d]	X[e] X[f] X[g]	
Informed consent	X							
Inclusion/exclusion criteria, subject demographics	X							
Medical/spinal cord injury history	X							
Physical examination	X[h]			X		X	X	
Full neurological examination	X						X	
Abbreviated neurological examination		X	X	X	X	X		X
American spinal injury association (ASIA) scale	X						X	
12-Lead electrocardiogram (ECG)	X						X	
Quantitative Assessment of Neuropathic Pain		X					X	
Clinical laboratories[i]	X						X	
Pregnancy test	X[j]						X[j]	
Adverse events		X	X	X	X	X	X	X
Prior/concurrent medications/nondrug treatments	X	X	X	X	X	X	X	X
Study treatment dispensing/dosing		X	X	X	X	X	X	
Vital signs/weight/edema/DVT assessment[k]	X	X	X	X	X	X	X	X
Subject-Completed Assessments/Questionnaires								
Neuropathic pain screening tool (ID Pain)	X							
Daily pain/sleep interference rating scale[l]	X	X	X	X	X	X	X	
Modified brief pain inventory (10-item)		X					X	
Medical outcomes study sleep scale (MOS-SS)		X					X	
Hospital anxiety and depression scale (HADS)		X					X	
Neuropathic pain symptom inventory (NPSI)		X					X	
Pain catastrophizing scale (PCS)		X						
Patient global impression of change (PGIC)							X	
Patient health questionnaire-8 (PHQ-8)	X							
Sheehan-suicidality tracking scale[m]	X	X	X	X	X	X	X	X

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Study Period	Screening	Double Blind Treatment Phase						Follow-Up
	V1 to V2: Up to 2 Weeks	V2 to V4: 4-Week Dose Adjustment		V4 to V7: 12-Week Maintenance			V7 to 1 Week After V7: 1-Week Taper	1-Week Off-Treatment
Clinic Visit	V1	V2	V3	V4	V5	V6	V7	V8
	Screening	Randomization					Termination[a]	Follow-Up[a]
Week in Study	-2	0	2	4	8	12	16	18
Study Day[b]	-14	1	15	29	57	85	113	127

CRP = C-reactive protein; DVT = Deep vein thrombosis; ECG = Electrocardiogram; ID = Identification; min = Minute; V = Visit.

a. Whenever a subject discontinued at any time from the study, or completed the maintenance phase, the subject returned for a termination visit and entered the 1 week taper phase, followed by a follow-up visit, as applicable.
b. All study visits were to occur within ±3 calendar days of the scheduled study day.
c. On Day 7 and Day 21, all subjects were contacted by telephone for a dose adjustment assessment.
d. Telephone contact was initiated with the subject 2 weeks after Visits 4, 5, and 6 to ensure compliance with daily diaries and study drug regimen, and to record any adverse events (AE), concomitant medications, and nondrug treatments. Also, an unplanned visit may have been scheduled for dose reduction, if necessary.
e. On Day 115, subjects were to be contacted by telephone to switch to taper Bottle B on Days 116 and 117.
f. On Day 117, subjects were to be contacted by telephone to switch to taper Bottle C on Days 118 and 119.
g. On Day 120, the day after the last dose of taper treatment, all subjects were contacted by telephone to confirm and to record final dates of treatment.
h. New York Heart Association (NYHA) classification was done at Visit 1 as part of the physical examination.
i. Fasting status for labs. CRP and estimated creatinine clearance were measured at Visit 1 only. If estimated serum creatinine clearance was <60 mL/min, at the Investigator's discretion, a serum sample and a 24-hour urine collection may have been obtained at an unplanned visit.
j. Serum pregnancy test was to be done on all females at Visits 1 and 7.
k. If the subject's disability did not allow the subject to be weighed safely it was permissible to indicate an estimated weight on the Case Report Form (CRF), and this was also to be noted in the source documents.
l. Daily diaries were dispensed to subjects at Visit 1 to complete at home throughout treatment period. Additional daily diaries were dispensed to subjects as needed. All other questionnaires were to be completed during clinic visits.
m. The Sheehan-Suicidality Tracking Scale (Sheehan-STS) has 2 versions. The "Lifetime Assessment" version was administered at Screening and the "Since Last Visit" version was used for all other visits. This scale may have been administered either by a clinician or subject through self-report.

Number of Subjects (Planned and Analyzed): The study planned to enroll a total of 200 subjects. A total of 280 subjects were screened, 220 subjects were randomized to study treatment (2 subjects in Chile, 15 subjects in China, 4 subjects in Colombia, 11 subjects in the Czech Republic, 7 subjects in Hong Kong, 18 subjects in India, 59 subjects in Japan, 11 subjects in the Philippines, 17 subjects in the Russian Federation, and 76 subjects in the US) (112 subjects in the pregabalin group and 107 subjects in the placebo group). One subject did not receive any study medication, hence the number of randomized subjects was different from the number of treated subjects.

Diagnosis and Main Criteria for Inclusion: Male and nonpregnant, nonlactating, postmenopausal, or surgically sterilized female subjects aged at least 18 years must have had a documented diagnosis of SCI for at least 12 months with an American Spinal Injury Association (ASIA) Impairment Scale grade of A, B, C, or D. Subjects also had to complete at least 4 daily pain diary entries during the 7 days prior to Baseline with an average score of ≥4 on the 11-point rating scale for pain. Subjects with any neurologic disorder, preexisting myelopathy, or severe pain unrelated to the SCI injury were to be excluded from the study.

Study Treatment: Subjects were randomized to study treatment at Visit 2 for pregabalin 150 mg/day to 600 mg/day (starting at 150 mg/day), or placebo in a ratio of 1:1. All randomized subjects took study drug twice a day (BID), once in the morning and once in the evening. Pregabalin was permitted to be taken with or without food. All study visits were to occur within ±3 calendar days of the scheduled study day.

All randomized subjects entered a 4-week double-blind dose adjustment phase. During the adjustment phase, subjects were assessed weekly and doses of pregabalin and matching placebo were adjusted in a blinded manner. Subjects randomized to placebo received placebo for the entire double-blind treatment phase. Subjects randomized to the pregabalin treatment group began treatment at 150 mg/day.

Following the end of the adjustment phase at Visit 4, subjects were at their optimized dose of pregabalin (150 mg/day, 300 mg/day, 450 mg/day, or 600 mg/day) or placebo, and remained at this maintenance dose throughout the next 12 weeks of the study. However, if intolerable adverse events (AEs) occurred during the maintenance phase, dosage may have been reduced by 1 level on 1 occasion.

Efficacy Endpoints:

Primary Efficacy Endpoint:

- Duration adjusted average change (DAAC) derived from the subject's daily pain diary, where pain was measured on an 11-point rating scale from 0 (no pain) to 10 (worst possible pain).

Secondary Efficacy Endpoints:

- Endpoint mean pain score;
- Weekly mean pain score;

- 30% and 50% responder rates;
- Endpoint mean sleep interference score;
- Modified Brief Pain Inventory Interference Scale (10-Item) (mBPI-10);
- Hospital and Anxiety Depression Scale (HADS);
- Medical Outcomes Study (MOS) Sleep Scale;
- Neuropathic Pain Symptom Inventory (NPSI);
- Patient Global Impression of Change (PGIC);
- Quantitative Assessment of Neuropathic Pain (QANeP)

Safety Evaluations:

The primary safety parameter was discontinuation due to AE: a proportion of subjects who discontinued from the study due to an AE were calculated for each treatment group. Relative risk and risk difference with 95% confidence interval were calculated between each pregabalin regimen and placebo.

Summaries by treatment group of AEs, clinical laboratory data, physical examination, vital signs, neurological data, Patient Health Questionnaire-8 (PHQ-8), and Sheehan-Suicidality Tracking Scale (Sheehan-STS) were provided, but no inferential testing was done.

Parameters evaluated by AE monitoring were: clinical safety laboratory values and vital signs (heart rate, blood pressure [BP] and temperature), 12-lead electrocardiograms (ECGs), ASIA impairment scale, suicidality, and physical examinations.

Statistical Methods:

Data Sets Analyzed:

The intent-to-treat (ITT) population was defined as all subjects randomized to at least 1 dose of study medication. The modified intent-to-treat (mITT) population was the subset of the ITT population that included all ITT subjects except the 8 subjects who were randomized before flexible-dose adjustment (12 February 2008). The mITT population was used for the primary efficacy analysis and for the secondary analyses unless otherwise specified. The Per Protocol (PP) population was defined as all mITT subjects who completed the full double-blind phase treatment, had medication compliance within 80-120% during double-blind treatment, and had no other significant protocol violations.

The safety population included every subject that signed an informed consent and had exposure to study medication and had at least one safety assessment.

A selected number of efficacy analyses were repeated on the ITT population and the PP population. All tests were performed at the 0.05 level.

The safety population included every subject who signed the informed consent form and had exposure to study medication and at least 1 safety assessment.

Pooling of Sites:

For all efficacy analyses that included a site effect or stratification by site, site pools replaced sites. The strategy for pooling of sites were based on the number of mITT subjects for each site and the geographic location of the sites. The final pooling of a site was determined after enrollment had been completed and the last subject was randomized to study treatment but before the database was locked and the blind was broken. Table 2 shows the final pooling of the participating sites into three regions: America, Asia, and Europe:

Table 2. Final Pooling of the Participating Sites

Region	Country Name	Number of Subjects
All subjects		219
America	All in the region	81
	Chile	2
	Columbia	3
	United States	76
Asia	All in the region	110
	China	15
	Hong Kong	7
	India	18
	Japan	59
	Philippines	11
Europe	All in the region	28
	Czech Republic	11
	Russian Federation	17

Analysis Methods:

Continuous variables were analyzed with analysis of covariance (ANCOVA) to allow for control of clinically relevant covariates like Baseline pain severity and pooled center (centers pooled into 3 geographical regions [America, Asia, and Europe]). For pain-related data (including DAAC, Mean Pain Score, Mean Sleep Interference Score, and responders), the analyses included Pain Catastrophizing Scale (PCS) Total Score as a covariate. Categorical variables were analyzed by either Cochran-Mantel-Haenszel method when sufficient precision was present and an ordinal nature was inherent in the variable, or logistic regression likewise to allow for adjustment of clinically relevant covariates like Baseline pain severity and pooled center.

Analysis of the Primary Endpoint:

The primary analysis compared the DAAC between the pregabalin and placebo groups using an analysis of covariance model that included baseline severity (pain) and baseline PCS total scores, and pooled center as a fixed (class) cofactor.

For the primary outcome, the hypotheses were as follows:

- Null hypothesis: the mean DAAC for the pregabalin group = the mean DAAC for the placebo group;
- Alternative hypothesis: the mean DAAC for the placebo group differed from the mean DAAC for the pregabalin group.

For the primary hypothesis test comparing the mean DAAC for the pregabalin group to the mean DAAC for the placebo group, the decision rule was as follows: significance was to be declared if the 2-tailed test for the difference between treatment groups was significant at the 0.05 level ($p \leq 0.05$).

Analysis of Secondary Endpoints:

For the secondary efficacy outcomes the hypotheses were as follows:

- Null hypothesis: The distribution (eg, mean) of the measure for the pregabalin group was the same as the distribution of the measure for the placebo group;
- Alternative hypothesis: The distribution of the measure for the pregabalin group was different from the distribution of the measure for the placebo group.

Change from the Baseline score to the Endpoint Score in Mean Pain Score from the diary was performed using the modified baseline observation carried forward (mBOCF) approach for missing value imputation. In addition, the secondary analysis was a longitudinal analysis of weekly mean pain changes using repeated measures mixed models and comparing treatments at the last scheduled study week based on this model (to assess durability of treatment effect. As a secondary analysis, the weekly pain scores were analyzed using a mixed model ANCOVA.

Effects for treatment, pooled center, Baseline Mean Pain Score, and Baseline PCS (Pain Catastrophizing Scale) Total Score were included as covariates. The covariance structure was compound-symmetric. In addition, the same statistical model as used in the primary analysis was applied to the weekly pain scores using the last observation carried forward (LOCF) and the baseline observation carried forward (BOCF); the BOCF method was assigned to baseline scores to any subjects who did not complete the study, or who had no postbaseline observations.

Longitudinal analyses of Mean Sleep Interference Scores used repeated measures mixed models to obtain estimates and test treatment differences for each study week. The mBPI-10

(Modified Brief Pain Inventory Interference Scale [10-Item]), HADS-D, HADS-A, Medical Outcomes Study Sleep Scale (MOS-SS) subscales, Neuropathic Pain Symptom Inventory (NPSI) continuous scores, and QANeP items were summarized and evaluated for both within and between group differences in changes from Baseline for continuous data.

Analysis of Safety Endpoints:

Summaries by treatment group of AEs and clinical laboratory parameters were provided but no inferential testing was done. Summaries by treatment group of physical examination, vital signs (heart rate, blood pressure [in a sitting position], and temperature [performed at Visits 1 and 8]), ECGs, neurological data, Patient Health Questionnaire-8 (PHQ-8), and Sheehan-STS (Sheehan-Suicidality Tracking Scale) were provided, but no inferential testing was done.

RESULTS

Subject Disposition and Demography: A total of 220 subjects were assigned to study treatment: 112 subjects in the pregabalin group and 107 subjects in the placebo group were treated (Table 3). A total of 93 (83.0%) subjects in the pregabalin group and 91 (85.0%) subjects in the placebo group completed the study. Nineteen (17.0%) subjects in the pregabalin group and 16 (15%) subjects in the placebo group discontinued from the study. The most frequently occurring reason for discontinuation from the study was an AE in both treatment groups: (8 [7.1%] and 8 [7.5%] subjects in the pregabalin and placebo groups, respectively). The data set analyzed are presented in Table 4.

Table 3. Subject Disposition – Safety Population

No. (%) of Subjects	Pregabalin	Placebo
Screened (280)	-	-
Assigned to study treatment (220)	-	-
Treated	112	107[a]
Completed	93 (83.0)	91 (85.0)
Discontinued	19 (17.0)	16 (15.0)
Relation to study drug not defined	11 (9.8)	8 (7.5)
Insufficient clinical response	1 (0.9)	2 (1.9)
No longer willing to participate in study	3 (2.7)	3 (2.8)
Other	2 (1.8)	0
Protocol violation	5 (4.5)	3 (2.8)
Related to study drug	6 (5.4)	5 (4.7)
Adverse event	6 (5.4)	5 (4.7)
Not related to study drug	2 (1.8)	3 (2.8)
Adverse event	2 (1.8)	3 (2.8)

One subject was randomized to study treatment after the first dose of study drug was taken: the subject was randomized to placebo, but the actual drug taken was pregabalin. On this table this subject was included in the pregabalin group.
No. = Number.
a. The number of subjects randomized to study treatment was different from the number of treated subjects due to one subject who did not receive any study medication.

Table 4. Data Sets Analyzed

No. (%) of Subjects	Pregabalin	Placebo
Assigned to study treatment (220)		
Treated	112[a]	107[b]
Analyzed for efficacy		
Intent to treat (ITT)	112 (100.0)	107 (100.0)
Subjects excluded from ITT	0	1
Did not receive study medication	0	1
Modified intent to treat (MITT)	106 (94.6)	105 (98.1)
Subjects excluded from MITT	6	3
Excluded from ITT	0	1
Randomized before flexible-dose adjustment[b]	6	2
Per protocol (PP)	77 (68.8)	80 (74.8)
Subjects excluded from PP	34	29
Excluded from MITT	6	3
Did not complete double blind phase	18	16
Not ≥80 - ≤120% compliant	5	6
Had significant protocol deviation(s)	5	4
Analyzed for safety		
Adverse events	112 (100.0)	107 (100.0)
Laboratory data[c]	106 (94.6)	100 (93.5)
Safety population	112 (100.0)	107 (100.0)

One subject was randomized after the first dose of study drug was taken; the subject was randomized to placebo, but the actual drug taken was pregabalin. On this table this subject is included in the pregabalin group.
No. = Number; ITT = Intent to treat; MITT = Modified intent to treat; PP = Per protocol
a. The number of randomized subjects (assigned to study treatment) was different from the number of treated subjects due to 1 subject who had missing information about doses taken. This subject was randomized to placebo. The subject decided not to come back to the site after Visit 2 despite the multiple efforts of the site to contact the subject; therefore, no information after Visit 2 (including the medication bottles for accountability) was collected.
b. Change from fixed dosing to flexible dosing.
c. Subjects who were not included in the laboratory data analysis set did not have any on-treatment laboratory assessments.

The majority of subjects were male (176/219, 80.4%), and the most frequently participating race was Asian (110/219 subjects, 50.2%) (Table 5). Demographic characteristics were similar between the treatment groups.

Table 5. Demographic Characteristics - ITT Population

Parameter	Pregabalin N=111	Placebo N=108
Gender, n (%):		
Male	84 (75.7)	92 (85.2)
Female	27 (24.3)	16 (14.8)
Premenopausal	14	8
Postmenopausal	13	8
Age (years):		
Mean (SD)	46.1 (12.7)	45.6 (13.8)
Range (min - max)	22 - 72	19 - 81
Race, n (%):		
White	42 (37.8)	43 (39.8)
Black	6 (5.4)	8 (7.4)
Asian	57 (51.4)	53 (49.1)
Other	6 (5.4)	4 (3.7)
Ethnicity, n (%):		
Hispanic/Latino	13 (11.7)	7 (6.5)
Not Hispanic/Latino	98 (88.3)	101 (93.5)
Weight (kg):		
Mean (SD)	69.9 (16.0)	73.5 (17.8)
Range (min - max)	40.0 - 117.9	38.6 - 134.0
BMI (kg/m^2):		
Mean (SD)	23.9 (4.5)	24.8 (5.1)
Range (min - max)	13.5 - 38.9	14.0 - 44.8
Height (cm):		
Mean (SD)	170.6 (10.1)	171.7 (9.6)
Range (min - max)	142.8 - 193.0	143.8 - 203.0

Body mass index was calculated as weight/(height × 0.01)^2.
One subject was randomized after the first dose of study drug was taken: the subject was randomized to placebo, but the actual drug taken was pregabalin. On this table this subject was included in the placebo group.
BMI = Body mass index; ITT = Intent-to-treat population; N = Number of subjects; n = Number of subjects in category; Max = Maximum; Min = Minimum; SD = Standard deviation.

Efficacy Results:

Primary Evaluation: DAAC (mITT):

Treatment with pregabalin resulted in statistically significantly improved (p-value=0.0032) DAAC (based on the daily pain diary) over the 16-week double-blind period compared to placebo (mITT population; Table 6).

Table 6. Statistical Analysis (ANCOVA) and Summary of Duration Adjusted Average Change (DAAC) (mITT Population)

	N	n	Mean (SD)	Min, Max	LS Mean (SE)	Difference from Placebo		
						Diff (SE)	95% CI	p-value
Pregabalin	105	105	-1.64 (1.465)	-5.9, 1.5	-1.66 (0.157)	-0.59 (0.198)	(-0.98, -0.20)	0.0032
Placebo	106	106	-1.05 (1.446)	-4.7, 3.1	-1.07 (0.149)	NA	NA	NA

If (total postbaseline days) were ≥112 then DAAC = (weighted postbaseline mean - Baseline).
The LS means from the ANCOVA model with terms of baseline severity of pain and Baseline Pain Catastrophizing Scale (PCS) Total Score as covariates and pooled center and treatment as fixed (class) cofactors.
One subject was randomized after the first dose of study drug was taken: the subject was randomized to placebo, but the actual drug taken was pregabalin. On this table, this subject was included in the placebo group.
ANCOVA = Analysis of covariance; CI = Confidence interval; DAAC = Duration Adjusted Average Change; Diff = Difference; LOCF = Last observation carried forward; LS = Least squares; Max = Maximum; Min = Minimum; mITT = Modified intent to treat; N = Number of subjects in mITT Population; n = Number of subjects analyzed for this endpoint; NA = Not applicable; SD = Standard deviation; SE = Standard error.
DAAC = (weighted postbaseline mean - baseline) × ([total postbaseline days] / planned study duration) based on the subject's daily pain diary.

Key Secondary Endpoints:

Change From Baseline in Weekly Mean Pain Score at Endpoint (mITT, mBOCF):

The treatment with pregabalin resulted in a statistically significant (p-value=0.0066) decrease (improvement) from Baseline in Mean Pain Score at endpoint compared with placebo (mITT population, mBOCF; Table 7).

Table 7. Statistical Analysis (ANCOVA) and Summary of Changes From Baseline in Mean Pain Score at Endpoint (mBOCF) – mITT Population

	N	n	Mean (SD)	Min, Max	LS Mean (SE)	Difference From Placebo		
						Diff (SE)	95% CI	p-value
Pregabalin	105	105	-1.90 (1.906)	-7.0, 2.6	-1.92 (0.203)	-0.70 (0.255)	(-1.20, -0.20)	0.0066
Placebo	106	106	-1.18 (1.778)	-6.4, 4.0	-1.22 (0.192)	NA	NA	NA

Endpoint (mBOCF) was implemented for subjects who discontinued due to an AE or had no postbaseline observation, otherwise, Endpoint (LOCF) applied.
Endpoint LOCF, which corresponded to the last 7 days of diary data up to and including Week 16 and applied, if the Week 16 assessment was missing.
The LS means from ANCOVA model with terms of baseline severity of pain and baseline Pain Catastrophizing Scale (PCS) Total Score as covariates and pooled center and treatment as fixed (class) cofactors.
One subject was randomized after the first dose of study drug was taken; the subject was randomized to placebo, but the actual drug taken was pregabalin. On this table this subject is included in the placebo group.
ANCOVA = Analysis of covariance; CI = Confidence interval; Diff = Difference; LOCF = Last observation carried forward; LS = Least squares; Max = Maximum; mBOCF = Modified baseline observation carried forward; Min = Minimum; mITT = Modified intent to treat; N = Number of subjects in mITT population; n = Number of subjects analyzed for this endpoint; NA = Not applicable; SD = Standard deviation; SE = Standard error.
On the Daily Pain Rating Scale (DPRS), 0 = No pain and 10 = Worst possible pain.

Responders (≥30% Reduction From Baseline in Mean Pain Score):

The odds of subjects having ≥30% reduction from Baseline in Mean Pain Score at endpoint were statistically significantly improved (odds ratio [OR] =1.85, p-value=0.0390) in the pregabalin group compared to placebo (mITT population, LOCF; Table 8). During Weeks 1 through 16 the proportion of subjects in the pregabalin group with ≥30% reduction from Baseline in Mean Pain Score was greater than the proportion in the placebo group.

Table 8. Statistical Analysis (Logistic Regression) of Subjects With ≥30% Reduction From Baseline in Mean Pain Score (Responders) at Endpoint (LOCF) - mITT

	No.	Evaluable N	Responders n (%)	Difference From Placebo		
				Odds Ratio	95% CI for OR	p-value
Pregabalin	105	105	48 (45.7)	1.85	(1.032, 3.328)	0.0390
Placebo	106	105	33 (31.4)	NA	NA	NA

Endpoint (LOCF) corresponded to the last 7 days of diary data up to and including Week 16 and applied if the Week 16 assessment was missing.
Odds ratio and its 95% CI calculated by exponentiating the log OR and 95% CI that correspond to the treatment contrast in the Logistic Regression Model with pooled center and treatment as the categorical factors, and Mean Pain Score at baseline and baseline Pain Catastrophizing Scale (PCS) total score as the covariates.
One subject was randomized after the first dose of study drug was taken; the subject was randomized to placebo, but the actual drug taken was pregabalin. On this table this subject is included in the placebo group.
CI = Confidence interval; LOCF = Last observation carried forward; mITT = Modified intent to treat; No. or N = Number of subjects; n = Number of responders; NA = Not applicable; OR = Odds ratio.
Summary statistics based on subjects with both baseline and endpoint data.

Patient Global Impression of Change: Full Scale (mITT, LOCF):

Subjects in the pregabalin group had statistically significant (p-value=0.0006) improvements in the PGIC (full scale) at endpoint (mITT population, LOCF) compared to subjects receiving placebo (Table 9). A greater proportion of subjects in the pregabalin group showed improvements in the PGIC (binary scale, where "improved" = Very much improved or Much improved) at endpoint compared with subjects receiving placebo.

Table 9. Summary of Statistical Analysis: CMH of PGIC (Full Scale) at Endpoint (LOCF) – mITT

No. (%) of Subjects[a]	Pregabalin N=105	Placebo N=106
Total No. assessed	100 (95.2)	99 (93.4)
Very much improved	7 (7.0)	2 (2.0)
Much improved	33 (33.0)	25 (25.3)
Minimally improved	38 (38.0)	24 (24.2)
No change	19 (19.0)	40 (40.4)
Minimally worse	2 (2.0)	5 (5.1)
Much worse	0	3 (3.0)
Very much worse	1 (1.0)	0
p-value (pregabalin vs placebo)	0.0006	NA

Endpoint (LOCF) - last available postbaseline visit value more than Visit 7.
CMH test (with modified ridit transformation) for difference without collapsing categories, p-values adjusted for pooled center.
One subject was randomized after the first dose of study drug was taken; the subject was randomized to placebo, but the actual drug taken was pregabalin. On this table this subject is included in the placebo group.
CMH = Cochran-Mantel-Haenszel; LOCF = Last observation carried forward; mITT = Modified intent to treat; N = Number of subjects; NA = Not applicable; No. = Number; PGIC = Patient Global Impression of Change.
a. Percentages for total No. assessed calculated using N in the denominator; all other percentages were calculated using total No. assessed in the denominator.

Change From Baseline in Weekly Mean Sleep Interference Score at Endpoint (mITT, LOCF):

Treatment with pregabalin resulted in a statistically significant (p-value <0.0001) decrease (improvement) from Baseline in the weekly mean sleep interference score at endpoint compared with placebo (mITT population, LOCF; Table 10).

Table 10. Statistical Analysis (ANCOVA) and Summary of Changes From Baseline in Weekly Mean Sleep Interference Score at Endpoint (LOCF) – mITT Population

	N	n	Mean (SD)	Min, Max	LS Mean (SE)	Difference From Placebo		
						Diff (SE)	95% CI	p-value
Pregabalin	105	105	-1.97 (2.351)	-9.3, 4.0	-2.10 (0.206)	-1.08 (0.265)	(-1.60, -0.56)	<0.0001
Placebo	106	104	-0.98 (1.774)	-6.7, 3.0	-1.02 (0.201)	NA	NA	NA

On the Daily Sleep Interference Rating Scale, 0 = Pain did not interfere with sleep and 10 = Pain completely interfered (unable to sleep due to pain).
Endpoint (LOCF) corresponded to the last 7 days of diary data up to and including Week 16 and applied if the Week 16 assessment was missing.
The LS means from the ANCOVA model with terms of baseline sleep interference score as a covariate and pooled center and treatment as fixed (class) cofactors.
One subject was randomized after the first dose of study drug was taken; the subject was randomized to placebo, but the actual drug taken was pregabalin. On this table this subject is included in the placebo group.
ANCOVA = Analysis of covariance; CI = Confidence interval; Diff = Difference; LOCF = Last observation carried forward; LS = Least squares; Max = Maximum; Min = Minimum; mITT = Modified intent to treat; N = Number of subjects in mITT population; n = Number of subjects analyzed for this endpoint; NA = Not applicable; SD = Standard deviation; SE = Standard error.

Other Secondary Endpoints:

Secondary Analyses of Duration Adjusted Average Change:

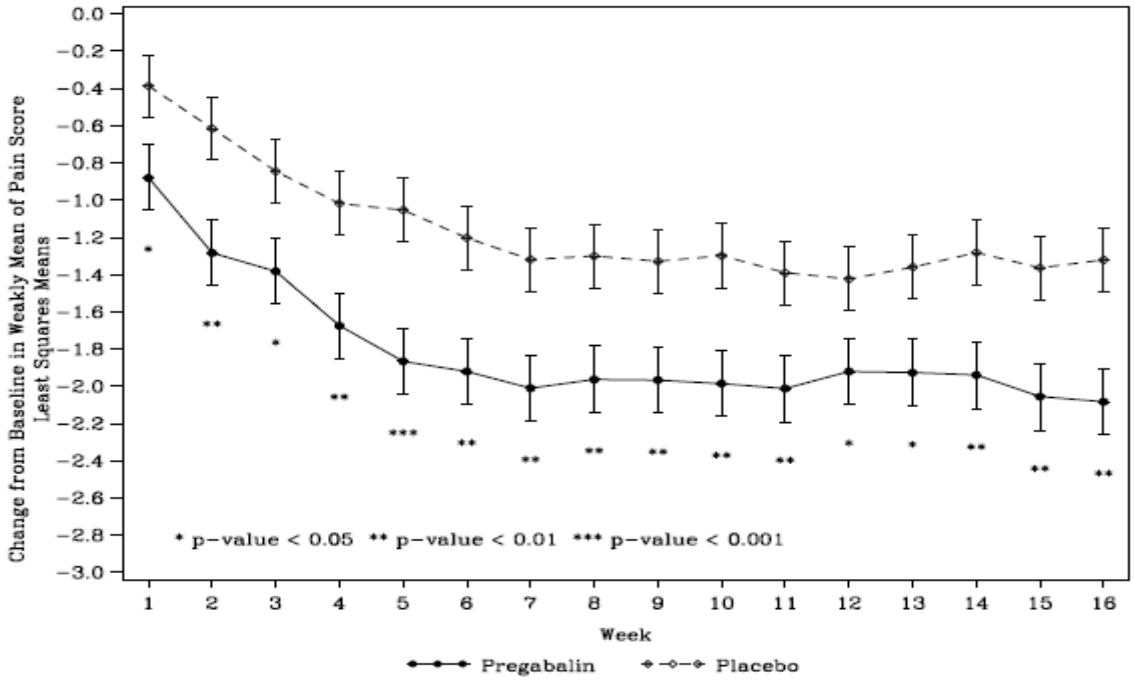
In an analysis of DAAC by smoking status, treatment with pregabalin statistically significantly improved DAAC compared to placebo for ex-smokers (p-value=0.0345) but not for current smokers or those who had never smoked. In an analysis of DAAC adjusted for smoking status and treatment by smoking status interaction, treatment with pregabalin statistically significantly improved DAAC compared to placebo (p-value=0.0012).

In an analysis of DAAC by SCI history, treatment with pregabalin statistically significantly improved DAAC compared to placebo for those with incomplete injuries (p-value=0.0186) but not for those with complete injuries; In an analysis of DAAC adjusted for SCI history and treatment by SCI history interaction, treatment with pregabalin statistically significantly improved DAAC compared to placebo (p-value=0.0034).

Changes From Baseline in Weekly Mean Pain Score by Week (ITT):

Using a mixed model for repeated measures (MMRM) analysis, treatment with pregabalin resulted in statistically significant (p-values≤0.0328) decreases (improvements) from Baseline in Mean Pain Scores compared to placebo for Weeks 1 through 16, Figure 1 (ITT population; Table 11).

Figure 1. Least Squares Mean Changes (±SE) From Baseline in Weekly Mean Pain Score (ITT Population)



On the Daily Pain Rating Scale (DPRS), 0 = No pain and 10 = Worst possible pain.
ITT = Intent to treat; LS = Least squares; SE = Standard error.

Table 11. Statistical Analysis (MMRM) and Summary of Changes From Baseline in Weekly Mean Pain Scores – ITT

	N	n	Mean (SD)	Min, Max	LS Mean[a] (SE)	Difference From Placebo[a]		
						Diff (SE)	95% CI	p-value
Week 1								
Pregabalin	111	111	-0.85 (1.04)	-4.9, 1.6	-0.88 (0.18)	-0.49 (0.23)	(-0.94, -0.05)	0.0295
Placebo	108	107	-0.38 (0.89)	-3.4, 2.0	-0.39 (0.17)	NA	NA	NA
Week 2								
Pregabalin	111	110	-1.26 (1.21)	-5.1, 1.1	-1.28 (0.18)	-0.67 (0.23)	(-1.11, -0.22)	0.0033
Placebo	108	105	-0.62 (1.30)	-4.7, 2.0	-0.61 (0.17)	NA	NA	NA
Week 3								
Pregabalin	111	107	-1.35 (1.35)	-5.1, 3.0	-1.38 (0.18)	-0.54 (0.23)	(-0.98, -0.09)	0.0185
Placebo	108	105	-0.86 (1.35)	-5.0, 2.0	-0.84 (0.17)	NA	NA	NA
Week 4								
Pregabalin	111	107	-1.64 (1.61)	-6.3, 3.4	-1.67 (0.18)	-0.66 (0.23)	(-1.10, -0.21)	0.0040
Placebo	108	103	-1.03 (1.53)	-6.5, 2.9	-1.02 (0.17)	NA	NA	NA
Week 5								
Pregabalin	111	105	-1.87 (1.73)	-6.9, 2.7	-1.86 (0.18)	-0.81 (0.23)	(-1.26, -0.36)	0.0004
Placebo	108	101	-1.07 (1.50)	-6.1, 3.0	-1.05 (0.17)	NA	NA	NA
Week 6								
Pregabalin	111	105	-1.89 (1.90)	-7.0, 1.7	-1.92 (0.18)	-0.72 (0.23)	(-1.17, -0.27)	0.0018
Placebo	108	99	-1.22 (1.72)	-6.9, 3.0	-1.20 (0.17)	NA	NA	NA
Week 7								
Pregabalin	111	103	-2.02 (1.86)	-7.0, 1.9	-2.01 (0.18)	-0.69 (0.23)	(-1.14, -0.24)	0.0027
Placebo	108	98	-1.34 (1.75)	-6.1, 3.0	-1.32 (0.17)	NA	NA	NA
Week 8								
Pregabalin	111	101	-1.96 (1.82)	-7.3, 2.4	-1.96 (0.18)	-0.66 (0.23)	(-1.11, -0.21)	0.0041
Placebo	108	97	-1.32 (1.82)	-6.4, 3.0	-1.30 (0.17)	NA	NA	NA
Week 9								
Pregabalin	111	98	-1.99 (1.81)	-7.0, 2.7	-1.97 (0.18)	-0.64 (0.23)	(-1.09, -0.18)	0.0058
Placebo	108	97	-1.37 (1.75)	-6.9, 3.0	-1.33 (0.17)	NA	NA	NA
Week 10								
Pregabalin	111	97	-2.03 (1.75)	-7.0, 3.3	-1.98 (0.18)	-0.69 (0.23)	(-1.14, -0.23)	0.0031
Placebo	108	91	-1.32 (1.81)	-6.3, 3.1	-1.30 (0.17)	NA	NA	NA
Week 11								
Pregabalin	111	96	-2.04 (1.82)	-7.0, 3.4	-2.01 (0.18)	-0.62 (0.23)	(-1.08, -0.17)	0.0076
Placebo	108	90	-1.43 (1.84)	-6.6, 4.0	-1.39 (0.17)	NA	NA	NA

Table 11. Statistical Analysis (MMRM) and Summary of Changes From Baseline in Weekly Mean Pain Scores – ITT

	N	n	Mean (SD)	Min, Max	LS Mean[a] (SE)	Difference From Placebo[a]		
						Diff (SE)	95% CI	p-value
Week 12								
Pregabalin	111	96	-1.90 (1.83)	-7.1, 2.4	-1.92 (0.18)	-0.50 (0.23)	(-0.95, -0.04)	0.0328
Placebo	108	91	-1.44 (1.93)	-6.7, 4.0	-1.42 (0.17)	NA	NA	NA
Week 13								
Pregabalin	111	93	-2.02 (1.76)	-7.0, 0.9	-1.93 (0.18)	-0.57 (0.23)	(-1.02, -0.11)	0.0150
Placebo	108	91	-1.39 (1.92)	-7.1, 4.0	-1.36 (0.17)	NA	NA	NA
Week 14								
Pregabalin	111	93	-2.00 (1.76)	-6.9, 0.7	-1.94 (0.18)	-0.66 (0.23)	(-1.11, -0.20)	0.0048
Placebo	108	92	-1.34 (1.89)	-6.4, 4.0	-1.28 (0.17)	NA	NA	NA
Week 15								
Pregabalin	111	93	-2.09 (1.80)	-7.0, 0.7	-2.05 (0.18)	-0.69 (0.23)	(-1.15, -0.24)	0.0030
Placebo	108	92	-1.41 (1.85)	-6.4, 4.0	-1.36 (0.17)	NA	NA	NA
Week 16								
Pregabalin	111	89	-2.17 (1.78)	-7.0, 1.0	-2.08 (0.18)	-0.76 (0.23)	(-1.22, -0.30)	0.0011
Placebo	108	90	-1.36 (1.87)	-6.4, 4.0	-1.32 (0.17)	NA	NA	NA

On the Daily Pain Rating Scale (DPRS), 0 = No pain and 10 = Worst possible pain.
A longitudinal analysis of weekly mean changes using repeated measures mixed models which compared treatments at each week and the last scheduled study week based on this model.
Effects for treatment, pooled center, time (week), Baseline pain score, Baseline Pain Catastrophizing Scale (PCS) Total Score and treatment by time interaction are included as covariates. The covariance structure is compound symmetric.
One subject was randomized after the first dose of study drug was taken; the subject was randomized to placebo, but the actual drug taken was pregabalin. On this table this subject is included in the placebo group.
CI = Confidence interval; Diff = Difference; ITT = Intent to treat; LS = Least squares; Max = Maximum; Min = Minimum; MMRM = Mixed model for repeated measures; N = Number of subjects in ITT Population; n = Number of subjects analyzed for this endpoint; NA = Not applicable SD = Standard deviation; SE = Standard error.
a. Subjects with missing Baseline Pain Catostrophisizing Scale (PCS) Total Score (including all subjects randomized before flexible-dose adjustment) were not included in the analyses.

Responders (≥50% Reduction From Baseline in Mean Pain Score):

The odds of subjects having ≥50% reduction from Baseline in Mean Pain Score at endpoint were statistically significantly improved (OR =2.24, p-value=0.0256) in the pregabalin group compared with placebo (mITT population, LOCF; Table 12). Analyses of subjects with ≥50% reduction from Baseline in Mean Pain Score at Endpoint for other populations were consistent with the results in the mITT (LOCF) population.

Table 12. Statistical Analysis (Logistic Regression) of Subjects With ≥50% Reduction From Baseline in Mean Pain Score (Responders) at Endpoint (LOCF) - mITT Population

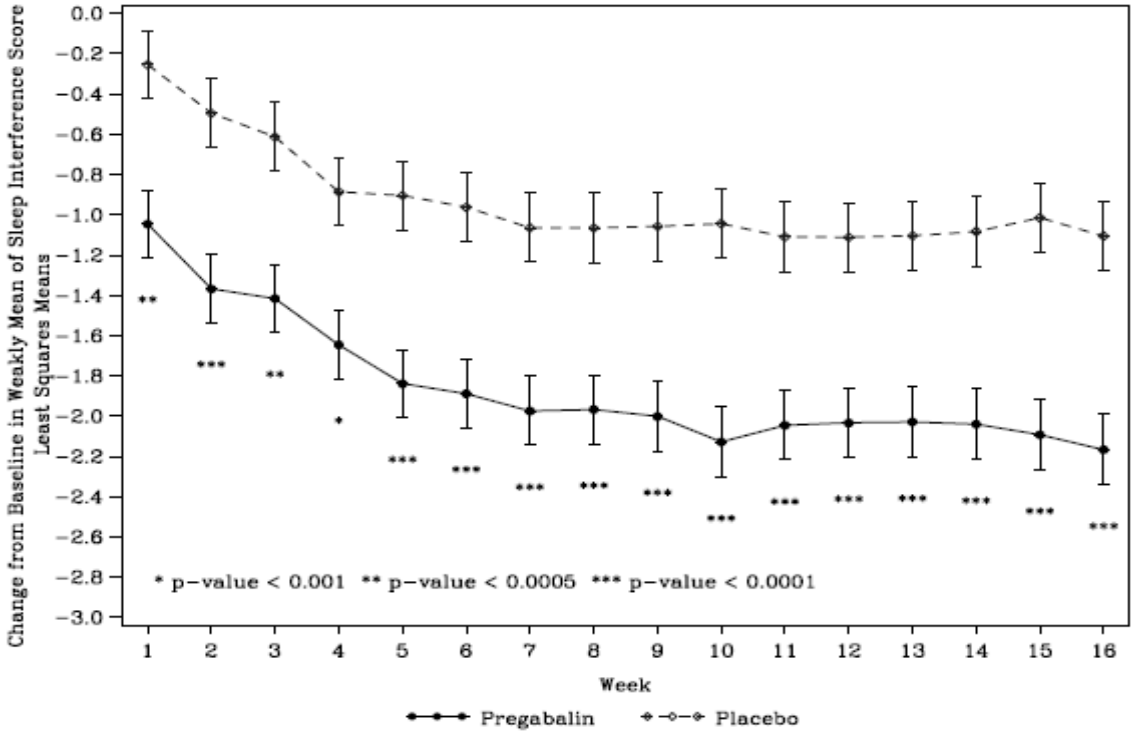
	No.	Evaluable N	Responders n (%)	Difference From Placebo		
				Odds Ratio	95% CI for OR	p-value
Pregabalin	105	105	31 (29.5)	2.24	(1.103, 4.546)	0.0256
Placebo	106	105	16 (15.2)	NA	NA	NA

CI = Confidence interval; LOCF = Last observation carried forward; mITT = Modified intent to treat; No. or N = Number of subjects; n = Number of responders; NA = Not applicable; OR = Odds ratio
Endpoint (LOCF) corresponded to the last 7 days of diary data up to and including Week 16 and applies if the Week 16 assessment was missing.
Odds ratio (OR) and its 95% CI calculated by exponentiating the log OR and 95% CI that corresponded to the treatment contrast in the Logistic Regression Model with pooled center and Treatment as the categorical factors, and Mean Pain Score at Baseline and Baseline Pain Catastrophizing Scale (PCS) Total Score as the covariates.
Summary statistics based on subjects with both Baseline and endpoint data.
One subject was randomized after the first dose of study drug was taken; the subject was randomized to placebo, but the actual drug taken was pregabalin. On this table this subject was included in the placebo group.

Changes From Baseline in Weekly Mean Sleep Interference Scores by Week (ITT):

Using an MMRM analysis, treatment with pregabalin resulted in statistically significant (p-values ≤0.0008) decreases (improvements) from Baseline in weekly mean sleep interference scores compared to placebo for Weeks 1 through 16, Figure 2. (ITT population; Table 13).

Figure 2. LS Mean Changes (±SE) From Baseline in Weekly Mean Sleep Interference Score (ITT Population)



ITT = Intent to treat; LS = Least squares; SE = Standard error; 0 = Pain did not interfere with sleep; 10 = Pain completely interfered (unable to sleep due to pain).

Table 13. Statistical Analysis (MMRM) and Summary of Changes From Baseline in Weekly Mean Sleep Interference Scores (ITT Population)

	N	n	Mean (SD)	Min, Max	LS Mean[a] (SE)	Difference From Placebo[a]		
						Diff (SE)	95% CI	p-value
Week 1								
Pregabalin	111	111	-0.96 (1.45)	-8.3, 4.4	-1.05 (0.17)	-0.79 (0.22)	(-1.23, -0.35)	0.0004
Placebo	108	106	-0.26 (0.85)	-3.6, 2.0	-0.25 (0.17)	NA	NA	NA
Week 2								
Pregabalin	111	110	-1.29 (1.63)	-7.1, 2.1	-1.37 (0.17)	-0.87 (0.22)	(-1.31, -0.43)	<0.0001
Placebo	108	104	-0.49 (1.17)	-4.8, 2.2	-0.49 (0.17)	NA	NA	NA
Week 3								
Pregabalin	111	107	-1.36 (1.68)	-7.1, 3.6	-1.41 (0.17)	-0.80 (0.22)	(-1.24, -0.36)	0.0004
Placebo	108	104	-0.61 (1.27)	-5.0, 3.3	-0.61 (0.17)	NA	NA	NA
Week 4								
Pregabalin	111	107	-1.59 (1.85)	-6.4, 4.0	-1.64 (0.17)	-0.76 (0.23)	(-1.20, -0.32)	0.0008
Placebo	108	102	-0.90 (1.45)	-4.7, 2.6	-0.88 (0.17)	NA	NA	NA
Week 5								
Pregabalin	111	105	-1.81 (2.05)	-9.4, 2.6	-1.84 (0.17)	-0.94 (0.23)	(-1.38, -0.49)	<0.0001
Placebo	108	100	-0.91 (1.38)	-4.7, 2.4	-0.90 (0.17)	NA	NA	NA
Week 6								
Pregabalin	111	105	-1.86 (2.14)	-9.1, 1.9	-1.89 (0.17)	-0.93 (0.23)	(-1.37, -0.48)	<0.0001
Placebo	108	98	-0.99 (1.48)	-4.9, 1.9	-0.96 (0.17)	NA	NA	NA
Week 7								
Pregabalin	111	103	-1.98 (2.19)	-9.0, 2.3	-1.97 (0.17)	-0.91 (0.23)	(-1.35, -0.47)	<0.0001
Placebo	108	97	-1.10 (1.50)	-5.1, 2.0	-1.06 (0.17)	NA	NA	NA
Week 8								
Pregabalin	111	101	-1.97 (2.18)	-9.7, 3.0	-1.97 (0.17)	-0.90 (0.23)	(-1.35, -0.46)	<0.0001
Placebo	108	96	-1.11 (1.59)	-5.7, 2.7	-1.06 (0.17)	NA	NA	NA
Week 9								
Pregabalin	111	98	-2.03 (2.13)	-8.9, 3.9	-2.00 (0.17)	-0.94 (0.23)	(-1.39, -0.50)	<0.0001
Placebo	108	96	-1.11 (1.72)	-5.4, 3.1	-1.06 (0.17)	NA	NA	NA
Week 10								
Pregabalin	111	97	-2.18 (2.06)	-9.1, 3.6	-2.13 (0.17)	-1.08 (0.23)	(-1.53, -0.63)	<0.0001
Placebo	108	90	-1.12 (1.74)	-6.3, 2.6	-1.04 (0.17)	NA	NA	NA
Week 11								
Pregabalin	111	96	-2.08 (2.15)	-9.7, 3.9	-2.04 (0.17)	-0.94 (0.23)	(-1.39, -0.49)	<0.0001
Placebo	108	89	-1.20 (1.85)	-5.7, 3.0	-1.11 (0.17)	NA	NA	NA

Table 13. Statistical Analysis (MMRM) and Summary of Changes From Baseline in Weekly Mean Sleep Interference Scores (ITT Population)

	N	n	Mean (SD)	Min, Max	LS Mean[a] (SE)	Difference From Placebo[a]		
						Diff (SE)	95% CI	p-value
Week 12								
Pregabalin	111	96	-2.07 (2.21)	-9.0, 3.9	-2.03 (0.17)	-0.92 (0.23)	(-1.37, -0.47)	<0.0001
Placebo	108	90	-1.20 (1.75)	-5.7, 3.0	-1.11 (0.17)	NA	NA	NA
Week 13								
Pregabalin	111	93	-2.08 (2.21)	-7.4, 3.8	-2.03 (0.17)	-0.92 (0.23)	(-1.38, -0.47)	<0.0001
Placebo	108	90	-1.19 (1.82)	-6.0, 3.0	-1.10 (0.17)	NA	NA	NA
Week 14								
Pregabalin	111	93	-2.09 (2.13)	-7.4, 4.3	-2.04 (0.17)	-0.96 (0.23)	(-1.41, -0.51)	<0.0001
Placebo	108	91	-1.18 (1.83)	-6.7, 3.0	-1.08 (0.17)	NA	NA	NA
Week 15								
Pregabalin	111	93	-2.15 (2.10)	-8.9, 3.6	-2.09 (0.17)	-1.08 (0.23)	(-1.53, -0.63)	<0.0001
Placebo	108	91	-1.11 (1.83)	-6.7, 3.0	-1.01 (0.17)	NA	NA	NA
Week 16								
Pregabalin	111	89	-2.25 (2.24)	-9.3, 4.0	-2.17 (0.17)	-1.06 (0.23)	(-1.51, -0.61)	<0.0001
Placebo	108	89	-1.17 (1.82)	-6.7, 3.0	-1.10 (0.17)	NA	NA	NA

On the Daily Sleep Interference Rating Scale, 0 = Pain did not interfere with sleep and 10 = Pain completely interfered (unable to sleep due to pain).
A longitudinal analysis of weekly mean changes using repeated measures mixed models which compared treatments at each week and the last scheduled study week based on this model.
Effects for treatment, pooled center, time (week), Baseline pain score, Baseline Pain Catastrophizing Scale (PCS) Total Score and treatment by time interaction are included as covariates. The covariance structure is compound symmetric.
One subject was randomized after the first dose of study drug was taken; the subject was randomized to placebo, but the actual drug taken was pregabalin. On this table this subject is included in the placebo group.
CI = Confidence interval; Diff = Difference; ITT = Intent to treat; LS = Least squares; Max = Maximum; Min = Minimum; MMRM = Mixed model for repeated measures; N = Number of subjects in ITT Population; n = Number of subjects analyzed for this endpoint; NA = Not applicable SD = Standard deviation; SE = Standard error.
a. Subjects with missing Baseline PCS Total Scores were not included in the analyses.

Modified Brief Pain Inventory Interference Scale (10-Item) (mBPI-10) Total Score (mITT Population, LOCF):

Treatment with pregabalin resulted in a statistically significant (p-value=0.0438) decrease (improvement) from Baseline in mBPI-10 Total Score at endpoint compared with placebo (mITT population, LOCF; Table 14).

Quantitative Assessment of Neuropathic Pain (QANeP) (mITT Population, LOCF):

Treatment with pregabalin resulted in mean decreases (improvements) from Baseline in all QANeP items at endpoint compared with placebo except for temporal summation to tactile stimuli for below the neurological lesion level (below level) pain (mITT population, LOCF; Table 15).

Neuropathic Pain Symptom Inventory (NPSI) (mITT Population, LOCF):

Treatment with pregabalin resulted in a statistically significant (p-value=0.0440) decrease (improvement) from Baseline in the pressing spontaneous pain subscale of the neuropathic pain symptom inventory (NPSI) at endpoint compared to placebo (mITT population, LOCF). Treatment with pregabalin resulted in decreases (improvements) from Baseline in 9 of 10 individual questions of the NPSI at endpoint compared with placebo (mITT population, LOCF).

Based on the NPSI, greater proportions of pregabalin-treated subjects had improvements (decreases from Baseline) in numbers of brief pain attacks and improved duration of brief pain attacks compared with placebo-treated subjects.

Medical Outcomes Study-Sleep Scale MOS-SS (mITT Population, LOCF):

MOS-SS Continuous Subscale Scores (mITT Population, LOCF): Treatment with pregabalin resulted in statistically significant (p-values ≤0.0347) least squares (LS) mean decreases (improvements) from Baseline in the MOS-SS 9-Item Sleep Problems Index and the Sleep Disturbance and Awaken Short of Breath or With Headache Subscales compared with placebo at endpoint (mITT population, LOCF; Table 16). Treatment with pregabalin resulted in a statistically significant (p-value=0.0436) LS mean increase from Baseline in the MOS-SS Sleep Quantity Subscale compared with placebo at endpoint (mITT Population, LOCF).

MOS-SS Optimal Sleep Subscale (mITT Population, LOCF): The odds of subjects having optimal sleep based on the MOS-SS were statistically significantly improved (OR =2.81, p-value=0.0024) in the pregabalin group compared with placebo at endpoint (mITT population, LOCF; Table 17).

Hospital Anxiety and Depression Scale (mITT Population, LOCF)

Treatment with pregabalin resulted in a statistically significant (p-value=0.0279) LS mean decrease (improvement) from Baseline in the HADS-D compared with placebo at endpoint (mITT population, LOCF).

Table 14. Statistical Analysis (ANCOVA) and Summary of Changes From Baseline in mBPI-10 Total Score at Endpoint (LOCF) – mITT Population

	N	n	Mean (SD)	Min, Max	LS Mean (SE)	Difference From Placebo		
						Diff (SE)	95% CI	p-value
Pregabalin	105	100	-1.57 (2.193)	-6.9, 5.5	-1.60 (0.209)	-0.55 (0.269)	(-1.08, -0.02)	0.0438
Placebo	106	99	-1.10 (2.020)	-5.4, 4.0	-1.06 (0.204)	NA	NA	NA

Range of scores: 0 = Does not interfere to 10 = Completely interferes.
Endpoint (LOCF) - last available postbaseline visit value - more than Visit 7.
LS Means from ANCOVA model with terms of Baseline mBPI-10 Total Score as a covariate and pooled center and treatment as fixed (class) cofactors.
One subject was randomized after the first dose of study drug was taken; the subject was randomized to placebo, but the actual drug taken was pregabalin. On this table this subject is included in the placebo group.
ANCOVA = Analysis of covariance; CI = Confidence interval; Diff = Difference; LS = Least squares; LOCF = Last observation carried forward; Max = Maximum; mBPI-10 = Modified Brief Pain Inventory Interference Scale (10-Item); Min = Minimum; mITT = Modified intent to treat; N = Number of subjects in mITT Population; n = Number of subjects analyzed for this endpoint; NA = Not applicable; SD = Standard deviation; SE = Standard error.

Table 15. Statistical Analysis (ANCOVA) and Summary of Changes From Baseline in QANeP Items at Endpoint (LOCF) - mITT Population

	N	n	Mean (SD)	Min, Max	LS Mean (SE)	Difference From Placebo		
						Diff (SE)	95% CI	p-value
Static mechanical allodynia								
At/above level								
Pregabalin	105	37	-1.00 (2.449)	-7.0, 4.0	-1.23 (0.339)	-0.17 (0.448)	(-1.06, 0.72)	0.7103
Placebo	106	49	-1.16 (2.641)	-10.0, 5.0	-1.06 (0.304)	NA	NA	NA
Below level								
Pregabalin	105	79	-1.00 (2.689)	-9.0, 7.0	-1.32 (0.284)	-0.61 (0.340)	(-1.28, 0.06)	0.0747
Placebo	106	75	-0.31 (2.482)	-9.0, 8.0	-0.71 (0.268)	NA	NA	NA
Dynamic mechanical allodynia								
At/above level								
Pregabalin	105	37	-0.92 (1.706)	-6.0, 1.0	-0.90 (0.288)	-0.22 (0.379)	(-0.97, 0.54)	0.5689
Placebo	106	48	-0.81 (2.150)	-7.0, 7.0	-0.68 (0.258)	NA	NA	NA
Below level								
Pregabalin	105	79	-0.63 (2.354)	-6.0, 7.0	-0.91 (0.269)	-0.23 (0.322)	(-0.87, 0.41)	0.4764
Placebo	106	75	-0.33 (2.321)	-8.0, 8.0	-0.68 (0.253)	NA	NA	NA
Punctate hyperalgesia								
At/above level								
Pregabalin	105	37	-0.97 (2.598)	-8.0, 4.0	-1.25 (0.360)	-0.46 (0.474)	(-1.40, 0.48)	0.3362
Placebo	106	49	-0.82 (2.713)	-6.0, 6.0	-0.79 (0.321)	NA	NA	NA
Below level								
Pregabalin	105	79	-0.97 (2.364)	-8.0, 7.0	-1.12 (0.266)	-0.33 (0.321)	(-0.96, 0.31)	0.3113
Placebo	106	75	-0.44 (2.151)	-9.0, 6.0	-0.79 (0.253)	NA	NA	NA
Temporal summation to tactile stimuli								
At/above level								
Pregabalin	105	37	-1.59 (3.050)	-9.0, 7.0	-1.65 (0.410)	-0.60 (0.539)	(-1.67, 0.48)	0.2721
Placebo	106	49	-0.86 (2.363)	-5.0, 7.0	-1.05 (0.365)	NA	NA	NA
Below level								
Pregabalin	105	79	-0.53 (2.206)	-7.0, 5.0	-0.71 (0.282)	0.23 (0.337)	(-0.43, 0.90)	0.4906
Placebo	106	75	-0.76 (2.370)	-10.0, 4.0	-0.94 (0.266)	NA	NA	NA

Table 15. Statistical Analysis (ANCOVA) and Summary of Changes From Baseline in QANeP Items at Endpoint (LOCF) - mITT Population

	N	n	Mean (SD)	Min, Max	LS Mean (SE)	Difference From Placebo		
						Diff (SE)	95% CI	p-value
Cold allodynia								
At/above level								
Pregabalin	105	37	-0.38 (2.453)	-7.0, 5.0	-0.50 (0.358)	-0.48 (0.472)	(-1.42, 0.46)	0.3123
Placebo	106	48	0.02 (2.497)	-6.0, 8.0	-0.02 (0.322)	NA	NA	NA
Below level								
Pregabalin	105	79	-0.10 (2.122)	-7.0, 9.0	-0.30 (0.304)	-0.55 (0.368)	(-1.28, 0.18)	0.1360
Placebo	106	72	0.40 (2.663)	-10.0, 9.0	0.25 (0.292)	NA	NA	NA
Cold hyperalgesia								
At/above level								
Pregabalin	105	37	-0.81 (2.402)	-7.0, 5.0	-0.83 (0.414)	-0.44 (0.549)	(-1.53, 0.65)	0.4257
Placebo	106	47	-0.34 (3.074)	-8.0, 10.0	-0.39 (0.376)	NA	NA	NA
Below level								
Pregabalin	105	79	-0.06 (2.599)	-6.0, 10.0	-0.37 (0.341)	-0.53 (0.412)	(-1.34, 0.28)	0.2005
Placebo	106	72	0.42 (2.822)	-8.0, 10.0	0.16 (0.328)	NA	NA	NA

Endpoint (LOCF) - last available postbaseline visit value – more than Visit 7.
At/above level = At or above the neurological lesion level; Below level = Below the neurological lesion level.
LS Means from ANCOVA model with terms of Baseline QANeP score as a covariate and pooled center and treatment as fixed (class) cofactors.
One subject was randomized after the first dose of study drug was taken; the subject was randomized to placebo, but the actual drug taken was pregabalin. On this table this subject is included in the placebo group.
ANCOVA = Analysis of covariance; CI = Confidence interval; Diff = Difference; LS = Least squares; LOCF = Last observation carried forward; Max = Maximum; Min = Minimum; mITT = Modified intent to treat; n = number of subjects evaluable; NA = Not applicable; SD = Standard deviation; SE = Standard error; QaNeP = Quantitative Assessment of Neuropathic Pain.
Ratings ranged from 0 = No pain to 10 = Worst possible pain.

Table 16. Statistical Analysis (ANCOVA) and Summary of Changes From Baseline in MOS-SS Subscales at Endpoint (LOCF) – mITT Population

	N	n	Mean (SD)	Min, Max	LS Mean (SE)	Difference From Placebo		
						Diff (SE)	95% CI	p-value
9-Item sleep problems index								
Pregabalin	105	100	-10.82 (16.696)	-57.8, 31.1	-9.72 (1.678)	-4.89 (2.182)	(-9.19, -0.59)	0.0262
Placebo	106	95	-5.76 (16.205)	-63.9, 28.3	-4.83 (1.667)	NA	NA	NA
Sleep disturbance								
Pregabalin	105	100	-17.34 (25.250)	-80.0, 36.3	-16.00 (2.308)	-8.67 (2.985)	(-14.55, -2.78)	0.0041
Placebo	106	97	-8.04 (21.699)	-78.8, 53.8	-7.33 (2.272)	NA	NA	NA
Sleep adequacy								
Pregabalin	105	100	11.60 (27.256)	-60.0, 100.0	10.48 (2.701)	5.78 (3.492)	(-1.11, 12.66)	0.0998
Placebo	106	97	5.67 (28.828)	-70.0, 70.0	4.70 (2.660)	NA	NA	NA
Snoring								
Pregabalin	105	100	2.20 (25.882)	-60.0, 100.0	0.83 (2.704)	5.70 (3.501)	(-1.20, 12.61)	0.1048
Placebo	106	97	-4.74 (27.504)	-100.0, 100.0	-4.87 (2.665)	NA	NA	NA
Awaken short of breath or with a headache								
Pregabalin	105	100	-6.20 (22.328)	-100.0, 60.0	-4.76 (1.873)	-5.14 (2.417)	(-9.91, -0.37)	0.0347
Placebo	106	98	-0.20 (22.521)	-80.0, 100.0	0.38 (1.837)	NA	NA	NA
Sleep quantity								
Pregabalin	105	100	0.64 (1.418)	-3.0, 5.0	0.60 (0.146)	0.38 (0.189)	(0.01, 0.76)	0.0436
Placebo	106	98	0.18 (1.287)	-4.0, 4.0	0.21 (0.145)	NA	NA	NA
Somnolence								
Pregabalin	105	100	-0.80 (20.636)	-53.3, 46.7	-0.19 (2.143)	3.02 (2.770)	(-2.44, 8.49)	0.2761
Placebo	106	97	-4.88 (22.309)	-80.0, 60.0	-3.22 (2.103)	NA	NA	NA

Endpoint (LOCF) - last available postbaseline visit value – more than Visit 7.
LS Means from ANCOVA model with terms of Baseline subscale score as a covariate and pooled center and treatment as fixed (class) cofactors.
One subject was randomized after the first dose of study drug was taken; the subject was randomized to placebo, but the actual drug taken was pregabalin. On this table this subject is included in the placebo group.
ANCOVA = Analysis of covariance; CI = Confidence interval; Diff = Difference; LOCF = Last observation carried forward; LS = Least squares; Max = Maximum; Min = Minimum; mITT = Modified intent to treat; MOS-SS = Medical Outcomes Study – Sleep Scale; N = Number of subjects in mITT Population; n = Number of subjects analyzed for this endpoint; NA = Not applicable; SD = Standard deviation; SE = Standard error.

Table 17. Statistical Analysis (Logistic Regression) of MOS-SS Optimal Sleep Subscale at Endpoint (LOCF) – mITT Population

	No.	Evaluable N	Optimal Sleep n (%)	Difference From Placebo		
				Odds Ratio	95% CI for OR	p-value
Pregabalin	105	100	49 (49.0)	2.81	(1.443, 5.491)	0.0024
Placebo	106	99	30 (30.3)	NA	NA	NA

Endpoint (LOCF) - last available postbaseline visit value – more than Visit 7.
Summary statistics based on subjects with both Baseline and endpoint data.
Odds ratio and its 95% CI calculated by exponentiating the log odds ratio and 95% CI that correspond to the treatment contrast in the Logistic Regression Model with pooled center and treatment as the categorical factors, and Optimal Sleep Score at Baseline as the covariate.
One subject was randomized after the first dose of study drug was taken; the subject was randomized to placebo, but the actual drug taken was pregabalin. On this table this subject is included in the placebo group.
CI = Confidence interval; LOCF = Last observation carried forward; mITT = Modified intent to treat; MOS-SS = Medical outcomes study – Sleep Scale; No. = Number of subjects in mITT Population; N = Number of subjects analyzed for this endpoint; n = Number of responders; NA = Not applicable; OR = Odds ratio.

Safety Results:

A summary of treatment-emergent AEs (TEAEs) is provided in Table 18.

Table 18. Treatment-Emergent Adverse Events – Safety Analysis Set

	Pregabalin N=112		Placebo N=107	
	All-Causalities	Treatment-Related	All-Causalities	Treatment-Related
Number of AEs	381	218	229	79
Subjects with AEs	95	75	84	50
Subjects with SAEs	9	1	10	0
Subjects with severe AEs	10	3	11	3
Subjects discontinued due to AEs	8	6	8	5
Subjects with dose reduced or temporary discontinuation due to AEs	20	18	13	9

Includes data up to 999 days after last dose of study drug.
Except for the number of AEs subjects were counted only once per treatment in each row.
Serious Adverse Events - according to the Investigator's assessment.
One subject was randomized after the first dose of study drug was taken; the subject was randomized to placebo, but the actual drug taken was pregabalin. On this table this subject was included in the pregabalin group
AE = Adverse event; N = Number of subjects; No.= Number; SAE = Serious adverse event.

All-Causality TEAEs: The all-causality treatment-emergent AEs occurring in at least 5% of subjects by body system and preferred term are presented in Table 19.

The most frequently reported TEAEs in the pregabalin group were somnolence, dizziness, oedema peripheral, and nasopharyngitis. In the placebo group, the most frequently reported TEAEs were urinary tract infection, nasopharyngitis, constipation and dizziness.

Table 19. Summary of Treatment-Emergent Adverse Events Occurring in ≥5% by System Organ Class and Preferred Term (All Causalities) -Safety Analysis Set

MedDRA System Organ Class/ Preferred Term No. (%) of Subjects	Pregabalin N=112	Placebo N=107
Number of subjects with AEs	78 (69.6)	56 (52.3)
Eye disorders	7 (6.3)	0
Vision blurred	7 (6.3)	0
Gastrointestinal disorders	20 (17.9)	14 (13.1)
Constipation	6 (5.4)	6 (5.6)
Diarrhoea	6 (5.4)	5 (4.7)
Dry mouth	9 (8.0)	3 (2.8)
Nausea	6 (5.4)	3 (2.8)
General disorders and administration site conditions	33 (29.5)	12 (11.2)
Fatigue	10 (8.9)	3 (2.8)
Oedema	6 (5.4)	2 (1.9)
Oedema peripheral	15 (13.4)	5 (4.7)
Pain	6 (5.4)	2 (1.9)
Infections and infestations	24 (21.4)	23 (21.5)
Nasopharyngitis	13 (11.6	8 (7.5)
Urinary tract infection	12 (10.7)	17 (15.9)
Nervous system disorders	52 (46.4)	22 (20.6)
Dizziness	22 (19.6)	6 (5.6)
Headache	8 (7.1)	5 (4.7)
Somnolence	37 (33.0)	14 (13.1)
Psychiatric disorders	7 (6.3)	4 (3.7)
Insomnia	7 (6.3)	4 (3.7)

Subjects are counted only once per treatment for each row.
Includes data up to 999 days after last dose of study drug.
MedDRA (v 14.0) coding dictionary applied.
MedDRA = Medical Dictionary for Regulatory Activities; N = The total number of subjects who received the treatment; n = The number of subjects with an adverse event while on study treatment; No. = Number; v = Version.

Treatment-Related TEAEs:

Treatment-emergent AEs considered related to treatment by the Investigator occurring in ≥5% of subjects in either group are summarized Table 20. The most frequently reported treatment-related TEAEs in both treatment groups were somnolence and dizziness.

Table 20. Summary of Treatment-Emergent Adverse Events Occurring in ≥5% of Subjects by System Organ Class and Preferred Term (Treatment-Related) – Safety Analysis Set

MedDRA System Organ Class/ Preferred Term No. (%) of Subjects	Pregabalin N=112	Placebo N=107
Eye disorders		
Vision blurred	7 (6.3)	0
Gastrointestinal disorders		
Dry mouth	9 (8.0)	3 (2.8)
General disorders and administration site conditions		
Fatigue	8 (7.1)	1 (0.9)
Edema	6 (5.4)	1 (0.9)
Edema peripheral	13 (11.6)	3 (2.8)
Nervous system disorders		
Dizziness	20 (17.9)	6 (5.6)
Somnolence	37 (33.0)	14 (13.1)

Includes data up to 999 days after last dose of study drug.
One subject was randomized after the first dose of study drug was taken; the subject was randomized to placebo, but the actual drug taken was pregabalin. On this table this subject is included in the pregabalin group.
MedDRA (v14.0) coding used.
AEs and SAEs results are not separated out.
AE = Adverse event; MedDRA = Medical Dictionary for Regulatory Activities; No. = Number; N = Number of subjects; SAE = Serious adverse event; v = Version.

Serious Adverse Events:

In total, 9 (8%) and 10 (9.3%) subjects reported at least 1 serious adverse event (SAE) in the exemestane and tamoxifen groups, respectively (Table 21). The most frequently reported treatment-emergent SAEs in the pregabalin group was pneumonia. One subject experienced a severe treatment-related treatment-emergent SAE of hypoglycemia.

Table 21. Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term (All Causalities) - Safety Analysis Set

MedDRA System Organ Class/ Preferred Term No. (%) of Subjects	Pregabalin N=112	Placebo N=107
Number of subjects with SAEs	9 (8.0)	10 (9.3)
Cardiac disorders	1 (0.9)	0
Bradycardia	1 (0.9)	0
Prinzmetal angina	1 (0.9)	0
Ear and labyrinth disorders	0	1 (0.9)
Ear haemorrhage	0	1 (0.9)
Hepatobiliary disorders	1 (0.9)	1 (0.9)
Cholecystitis	0	1 (0.9)
Cholelithiasis	1 (0.9)	0
Infections and infestations	3 (2.7)	2 (1.9)
Osteomyelitis chronic	0	1 (0.9)
Pneumonia	3 (2.7)	0
Pyelonephritis acute	0	1 (0.9)
Urinary tract infection	0	1 (0.9)
Injury, poisoning and procedural complications	1 (0.9)	2 (1.9)
Fall	0	1 (0.9)
Head injury	0	1 (0.9)
Ulna fracture	1 (0.9)	0

Subjects are counted only once per treatment for each row.
Includes data up to 999 days after last dose of study drug.
MedDRA (v14.0) coding dictionary applied.
MedDRA = Medical Dictionary for Regulatory Activities; No. = Number; N = Number of subjects; SAE = Serious adverse event; v = Version.

Discontinuations due to AEs:

Permanent discontinuations due to AEs are summarized in Table 22. A total of 16 subjects were withdrawn from the study due to TEAEs: 8 subjects each in the placebo and pregabalin groups.

Table 22. Discontinuations Due to Treatment-Emergent Adverse Events - Safety Analysis Set

Serial No.	MedDRA System Organ Class/ Preferred Term	Start Day/ Stop Day[a]	Day of Last Dose	Severity	Outcome	Causality
Pregabalin						
1	Nervous system disorders/Somnolence	16/57	56	Mild	Resolved	Study drug
2	General disorder and administration site conditions/Edema peripheral	55/90	62	Moderate	Resolved	Study drug
3[b]	Infections and infestations/Pneumonia	71/99	71	Severe	Resolved	Other illness
4[b]	Metabolism and nutrition disorders/ Hypoglycemia	72/73	60	Severe	Resolved	Study drug
5[b]	Vascular disorders/Hypotension	36/38	36	Severe	Resolved	Concom. treatment
6	Nervous system disorders/Somnolence	23/38	36	Moderate	Resolved	Study drug
7	Respiratory, thoracic and mediastinal disorders/Choking sensation	8/[>16]	12	Moderate	Still Present	Study drug
8	Musculoskeletal and connective tissue disorders/Muscular weakness	8/32	21	Mild	Resolved	Study drug
Placebo						
9[b]	Infections and infestations/ Osteomyelitis chronic	23/29	34	Severe	Resolved	Other illness
10	General disorders and administration site conditions/Fatigue	2/5	5	Severe	Resolved	Study drug
	Injury, poisoning and procedural complications/Fall	2/5	5	Severe	Resolved	Study drug
	Nervous system disorders/Dizziness	2/5	5	Moderate	Resolved	Study drug
	Respiratory, thoracic and mediastinal disorders/Dyspnea	2/8	5	Mild	Resolved	Study drug
11	Psychiatric disorders/Depression	9/22	15	Moderate	Resolved	Study drug
12	Gastrointestinal disorders/ Abdominal pain upper	22/32	32	Moderate	Resolved	Study drug
13	Gastrointestinal disorders/ Abdominal pain lower	1/3	2	Mild	Resolved	Study drug
14*	Musculoskeletal and connective tissue disorders/Back pain	64/[>85]	78	Moderate	Still Present	Disease under study
15	Gastrointestinal disorders/Constipation	5/[>68]	59	Moderate	Still Present	Study drug
16	Psychiatric disorders/Panic disorder	16/[>43]	35	Moderate	Still Present	Other unknown

Values in brackets are imputed from incomplete dates and times.
AE = Adverse event; MedDRA = Medical Dictionary for Regulatory Activities (version 14.0); SAE = Serious adverse event; Concom = Concomitant.
a. Start and Stop Days of AE.
b. SAE (Investigator's assessment);

Dose Reductions or Temporary Discontinuations due to TEAEs:

In the pregabalin group, 20 subjects had dose reductions or temporary discontinuations due to all causalities TEAEs; and 18 subjects had dose reductions or discontinuations due to a treatment-related TEAEs (Table 18).

Deaths: There were no deaths among subjects who participated in this study.

Clinical Safety Laboratory Values, Vital Signs, ECGs and Physical Examinations:

Clinical Safety Laboratory Values: In clinical laboratory tests there were no notable differences between treatment groups with regard to abnormalities for any analyte except 1 subject who experienced a severe treatment-related treatment-emergent SAE of hypoglycemia which resulted in withdrawal while receiving pregabalin 225 mg.

Vital Signs: AEs related to vital signs occurred more frequently in the pregabalin group than in the placebo group (Table 23). Mean changes from Baseline to Week 16 in sitting BP values and pulse rate in both treatment groups were small and not clinically significant.

From Baseline to Week 16/early termination (ET) the mean changes in weight were +0.8 kg in the pregabalin group and -0.4 kg in the placebo group.

Table 23. Summary of Treatment-Emergent Adverse Events Related to Vital Signs (All Causalities)

Preferred Term No. (%) of Subjects	Pregabalin N=112	Placebo N=107
Hypertension	4 (3.6)[a]	2 (1.9)[b]
Blood pressure increased	1 (0.9)[c]	1 (0.9)
Hypotension	2 (1.8)[d, c]	0
Blood pressure decreased	1 (0.9)[d]	0
Orthostatic hypotension	1 (0.9)	0

All of these AEs were of mild or moderate intensity unless otherwise indicated.
Includes data up to 999 days after last dose of study drug.
One subject was randomized after the first dose of study drug was taken; the subject was randomized to placebo, but the actual drug taken was pregabalin. On this table this subject is included in the pregabalin group.
AE = Adverse event; MedDRA = Medical Dictionary for Regulatory Activities; No. = Number; N = Number of subjects; SAE = Serious adverse event; v = Version.
MedDRA (v14.0) coding used.
a. Two of these AEs were treatment-related.
b. One of these AEs was treatment-related.
c. One of these AEs was of severe intensity and considered an SAE.
d. This AE was treatment-related.

Electrocardiograms: One subject in the pregabalin group had SAEs of bradycardia and prinzmetal angina; both were considered of severe intensity and neither was considered related to treatment. At Week 16/ET, only one subject, who received pregabalin, had a clinically significant abnormal ECG (ST-T changes compatible with ischemia); this subject had the same finding at Screening and a history of myocardial infarction.

Physical Examinations: The most frequent findings at final physical examination in both treatment groups were related to skin; in general these findings were not clinically significant.

Other Safety Results:

The ASIA Impairment Scale: There were no clinically or statistically significant changes in the ASIA Impairment Scale from Screening to endpoint.

Suicidality: A total of 9 unique subjects (5 subjects in the pregabalin group and 4 subjects in the placebo group) reported suicidal ideation (per the C-CASA mapping) since the last visit at least once during Visits 3 through 8.

CONCLUSIONS:

This study demonstrated the efficacy of pregabalin (150-600 mg/day, dosed BID) compared with placebo for the treatment of central neuropathic pain associated with SCI based on reduction in pain (the primary endpoint) as well as pain interference with sleep, anxiety, and patient-reported improvements (secondary endpoints), similar to the results previously reported.

Pregabalin was safe and well-tolerated. AEs were consistent with the known safety profile of pregabalin and similar to those observed in other studies, with somnolence and dizziness being the most frequent adverse events.