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

PROTOCOL NO.: A0081007

PROTOCOL TITLE: A Randomized Placebo-Controlled Trial of the Efficacy and Safety of Pregabalin in the Treatment of Subjects With Neuropathic Pain Associated With Lumbo-Sacral Radiculopathy

Study Centers: 46 centers (2 in Belgium, 6 in Canada, 7 in Germany, 6 in Italy, 6 in Spain, 6 in Sweden, 3 in Turkey, and 10 in the United States).

Study Initiation and Final Completion Dates: 07 April 2005 to 19 June 2007

Phase of Development: Phase 3

Study Objectives:

Primary objective:

Evaluate the efficacy of pregabalin in relieving neuropathic pain in subjects with lumbo-sacral radiculopathy by assessing time to a meaningful increase in pain or discontinuation from the study during double-blind treatment.

Secondary objectives:

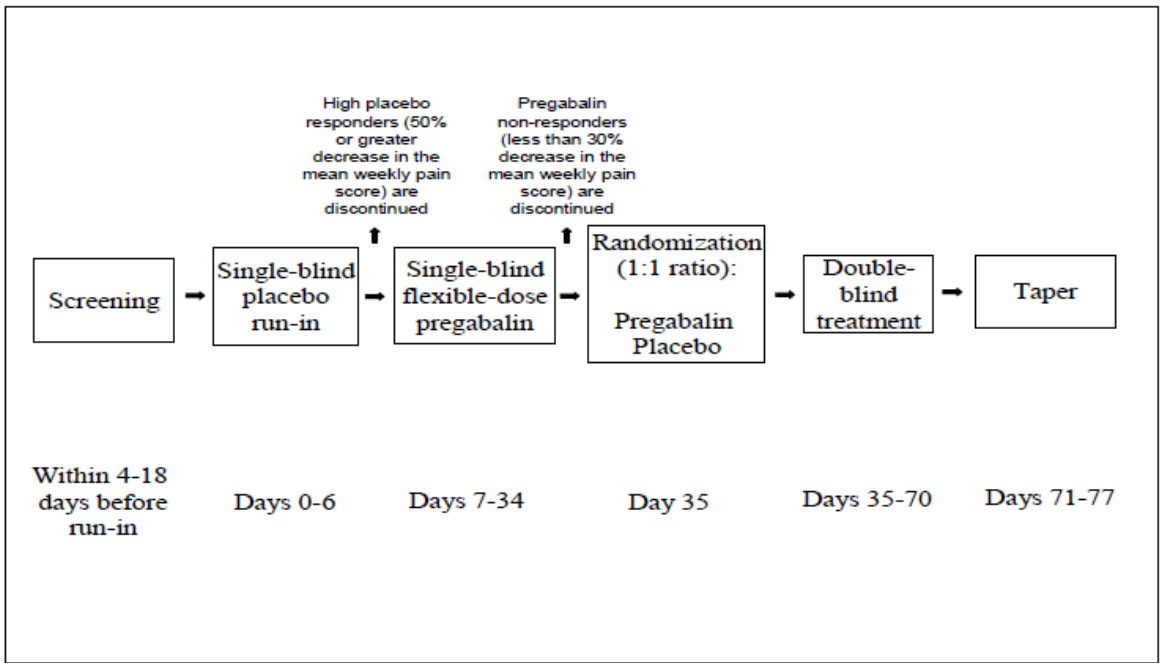
- Evaluate the safety and tolerability of pregabalin for the treatment of subjects with chronic neuropathic pain due to lumbo-sacral radiculopathy.
- Evaluate the responder rates at the end of single-blind pregabalin treatment.
- Evaluate the number of days subjects experience mild, moderate, and severe pain during screening, single-blind flexible-dose pregabalin treatment and double-blind treatment.
- Evaluate improvement in subject-reported sleep interference due to pain.
- Evaluate the impact of treatment on the subject-reported levels of mood disturbance and anxiety.
- Evaluate subject global impression of change.
- Evaluate subject satisfaction with treatment.

- Evaluate improvement in subject-reported levels of disability, work productivity, and other health outcomes measures.
- Evaluate the impact of pregabalin treatment on health care utilization.
- Evaluate the impact of prior back surgery on subject response during single-blind and double-blind treatment.

METHODS

Study Design: This was a randomized, placebo-controlled, multicenter trial designed to compare the efficacy of double-blind pregabalin versus placebo in the treatment of adult subjects with chronic neuropathic pain associated with lumbo-sacral radiculopathy. The study consisted of 5 phases as described in Figure 1. There were a total of 10 clinic visits; Visits 1(Day -18 to -4), 2 (Day 0), 3 (Day 7), 4 (Day 14), 5 (Day 21), 6 (Day 35), 7 (Day 42), 8 (Day 56), 9 (Day 70) and 10 (Day 77) plus contact by telephone on Days 28, 49 and 63. To exclude placebo responders, subjects who experienced a decrease of 50% or more in the mean weekly pain score during the placebo run-in phase were to be discontinued. In addition, only those subjects who responded to pregabalin treatment (≥30% decrease in the mean weekly pain score at the end of single-blind pregabalin treatment) were eligible to be randomized to double-blind pregabalin or placebo.

Figure 1. Study Design Overview



Number of Subjects (Planned and Analyzed): It was estimated that 850 subjects would need to be screened such that 765 subjects would enter the placebo run-in phase, 574 subjects would enter the single-blind pregabalin treatment phase, and at least 200 subjects would enter the double-blind treatment phase. A total of 544 subjects were screened. Of these, 378 subjects entered the placebo run-in phase, 363 subjects entered the single-blind

pregabalin treatment phase and 217 subjects entered the double-blind treatment phase. A total of 187 subjects completed the study (98 subjects in the pregabalin treatment group and 89 subjects in the placebo treatment group). Overall, 110 in the pregabalin group and 107 subjects in the placebo group were analyzed for efficacy (intent-to-treat [ITT]).

Diagnosis and Main Criteria for Inclusion: The study population included men and women (non-pregnant and using an effective method of contraception unless post-menopausal) from 18 to 100 years of age who had pain consistent with a diagnosis of chronic lumbo-sacral radiculopathy due to spinal stenosis or disk herniation. The radicular pain had to be present for at least 3 months, and the subject's pain had to be stable for at least 4 weeks.

Study Treatment: Pregabalin was provided as capsules (75, 150 and 300 mg) with a matching placebo capsule. Study treatment commenced with the 1-week single blind placebo run-in phase. During the 4-week single-blind pregabalin treatment phase, pregabalin was flexibly titrated within the 150 to 600 mg/day dose range to achieve an optimal balance between pain relief and tolerability. During the 5-week double-blind treatment phase, subjects randomized to pregabalin were to remain on the dose they had been on at the end of the single-blind pregabalin treatment phase; dose adjustments were not permitted. Subjects randomized to double-blind placebo were to taper off pregabalin over a 7-day period and then receive placebo for the remaining 4 weeks of the double-blind phase. Subjects were to taper off the study medication (pregabalin or placebo) after their last dose over a 7-day period.

Efficacy Endpoints:

Primary endpoint**:**

Time to a meaningful increase in pain or discontinuation from the study (for any reason) during double-blind treatment until the first day of the taper, regardless of how long the subject stayed in the study (Daily Pain Rating Scale).

Secondary endpoints: Secondary efficacy endpoints were as listed below:

- Responder rates at the end of single-blind pregabalin treatment.
- Weekly mean pain scores at the end of double-blind treatment.
- Number of days of mild, moderate, and severe pain during screening, single-blind treatment, and double-blind treatment.
- Daily Sleep Interference Scale.
- Medical Outcomes Study (MOS) Sleep Scale.
- Hospital Anxiety and Depression Scale (HADS).
- Generalized Anxiety-Visual Analog Scale (GA–VAS).

- Pain Treatment Satisfaction Scale (PTSS).
- Patient Global Impression of Change (PGIC).
- Modified Roland-Morris Disability Scale (RDQ).
- Work Productivity and Activity Impairement Questionnaire (WPAI).
- Euro Quality of Life (EQ-5D) Health State Profile and Visual Analog Scale (VAS).
- Lumbar Radiculopathy Pain Management Questionnaire.

Safety Endpoints:

- Adverse events (AEs).
- Concomitant pharmacological and non-drug treatments.
- Laboratory test results.
- Physical examination results.
- Vital signs.

Safety Evaluations:

Any AEs volunteered by the subject or observed by the investigator, were recorded throughout the study. Clinical laboratory safety evaluations and physical examinations were performed at screening and at the end of treatment (Day 70). Vital sign measurements (blood pressure, pulse, temperature, body weight) were measured at each clinic visit. At screening only, an electrocardiogram and a neurological examination were performed.

Statistical Methods:

Analysis Populations: Primary and secondary efficacy analyses were performed using the ITT population, defined as all randomized subjects who took at least 1 dose of study medication, and had at least 1 post-randomization efficacy assessment on any efficacy scale. Analyses of data from the single-blind pregabalin phase were based on all subjects who received single-blind treatment. Subjects were evaluable for safety if they received at least 1 dose of single-blind pregabalin.

Primary Efficacy Evaluation: The primary efficacy endpoint ie, a meaningful increase in pain was defined as a ≥1-point increase in the Daily Pain Rating Scale score when compared with the weekly mean pain score calculated at randomization (Day 35). To ensure that the 1-point change was not due to a short-term fluctuation in pain level and was clinically meaningful, subjects must also have had a weekly mean pain score at the end of double-blind treatment that had returned to within 30% of the subject's weekly mean pain score at the start of the study (screening). The use of rescue therapy for pain due to lumbo-sacral

radiculopathy during the double-blind treatment phase was also considered evidence of a meaningful increase in pain for analysis purposes. Subjects who did not fulfill these criteria for relapse were censored at the last observation of the Daily Pain Rating Scale. Time to event curves for pregabalin and placebo were plotted using Kaplan-Meier methods and compared using a Cox proportional hazard model that included factors to control for pooled study center, prior back surgery and baseline pain severity. The null hypothesis was to be rejected if the p-value for the treatment effect from the model was <0.05.

Secondary Efficacy and Health Outcomes Evaluations: For continuous outcomes analyzed at a single time point, an analysis of covariance (ANCOVA) model was used. Effects for treatment, pooled study center, and baseline pain score were included as covariates. MOS Optimal Sleep was analyzed using logistic regression analysis. Utility scores and VAS scores from the EQ-5D were summarized by 1-point intervals of the daily pain rating scale, and by pain categories of mild (<4), moderate (≥4 and <7), and severe (≥7) pain.

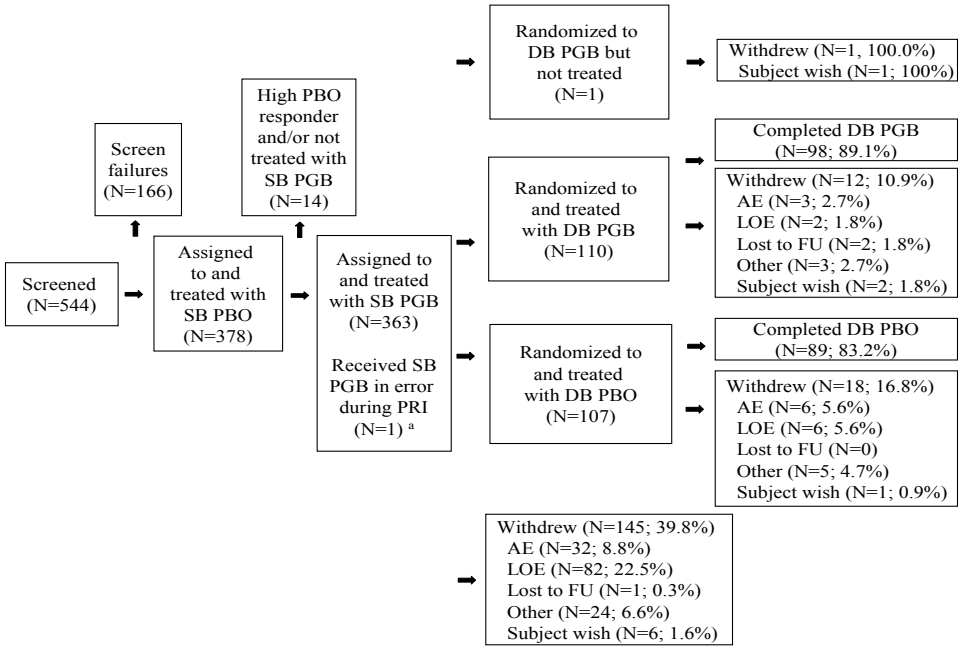
In addition, the weekly pain scores were analyzed using a repeated measures model with fixed effects of treatment, pooled center, week, and the treatment-by-week interaction. The baseline score was included as a covariate, and subject as a repeated measurement block within which the covariance structure was assumed to be compound symmetric. Correlations between continuous variables (between PGIC and changes from baseline in the Daily Pain Rating Scale and GA-VAS scores) were done using Pearson's correlation coefficient. Categorical variables were analyzed using the Cochran-Mantel-Haenszel (CMH) method, when sufficient precision was present and an ordinal nature was inherent in the variable, or logistic regression with adjustment for baseline pain and pooled study center, and possibly other clinically relevant covariates. Missing daily diary data values were imputed using the weekly mean for the week in which the values were missing. The imputation applied up to the last day of treatment. Efficacy endpoints used last observation carried forward (LOCF) to impute missing values.

Safety Evaluation: Safety data were summarized descriptively.

RESULTS

Subject Disposition and Demography: Subject disposition is shown in Figure 2. Data sets analyzed are summarized in Table 1.

Figure 2. Subject Disposition, All Subjects



Note: Percentages of subjects who withdrew from single-blind pregabalin are based on the number of subjects who received at least 1 dose of single-blind pregabalin. Percentages of subjects who withdrew from double-blind treatment are based on the number of subjects who received at least 1 dose of double-blind medication. One additional subject who was randomized to pregabalin but not treated is depicted separately.
AE=adverse event; DB=double-blind; FU=follow up; LOE=lack of efficacy; N=number of randomized subjects; PBO=placebo; PGB=pregabalin; PRI=placebo run-in; SB=single-blind
a: One subject was treated with single-blind pregabalin in error during the placebo run-in phase. The subject discontinued the study during the placebo run-in phase due to "other."

Table 1. Data Sets Analyzed

	Randomized Subjects		All Subjects (N=364)
	Pregabalin	Placebo	
	n	n	n
Received single-blind pregabalin[a]	NA	NA	364
Randomized to double-blind treatment[b]	111	107	NA
Received double-blind treatment[b]	110	107	
Analyzed for efficacy			
Full analysis set (ITT)[b]	110	107	NA
Excluded from ITT population			
Did not have valid BL or post-BL pain data[b]	1	0	NA
Evaluated for safety[b]			
Adverse events	110	107	364
Laboratory data	104	102	326

BL=baseline; ITT=intent-to-treat; N=number of randomized subjects; n=number of subjects meeting criteria; NA=not applicable

a One subject who was not assigned to single-blind pregabalin is included in this row because the subject received single-blind pregabalin (in error) during the placebo run-in phase. The subject discontinued the study during the placebo run-in phase.

b One subject who was randomized to pregabalin and had post-randomization efficacy data but did not receive any double-blind study medication was included in the ITT population. A second subject who was randomized to and treated with double-blind pregabalin but had no post-randomization efficacy data was excluded from the ITT population.

Among all subjects treated with at least 1 dose of single-blind pregabalin, approximately 50% of subjects were male, approximately 97% of subjects were white, the mean age was 52.6 years, and mean body mass index was 27.8 kg/m^2. Following randomization, the pregabalin and placebo treatment groups were generally well balanced with respect to demographic characteristics.

The majority (79.7%) of all subjects treated with at least 1 dose of single-blind pregabalin had a primary diagnosis of intervertebral disk protrusion. A primary diagnosis of lumbar spinal stenosis was reported for 15.4% subjects, with a further 11.0% subjects having a primary diagnosis of spinal column stenosis. Seventy-eight (21.4%) subjects had more than 1 primary diagnosis. Following randomization, the treatment groups were generally well balanced with respect to the primary cause of the subjects' lumbo-sacral radiculopathy.

Eighty-eight (24.2%) subjects previously received back surgery of some kind; 32 (8.8%) subjects received prior back surgery in the lumbar area.

At the end of the single-blind treatment period, the mean and median daily dose of pregabalin taken by subjects randomized to double-blind pregabalin was 445.9 and 600 mg, respectively, and the mean and median daily dose of pregabalin taken by subjects randomized to double-blind placebo was 410.0 and 300 mg, respectively.

Efficacy Results:

Primary efficacy results: Among subjects who responded to pregabalin after 4 weeks of single-blind treatment, those subsequently randomized to double-blind pregabalin were no

more or less likely than those randomized to double-blind placebo to experience a meaningful increase in pain over the 5-week double-blind treatment period (hazard ratio, 0.874; 95% CI, [0.520, 1.470]; p=0.6127). Detailed primary efficacy results are described in Table 2.

Table 2. Time to a Meaningful Increase in Pain (≥1-Point Increase in Pain Score or Discontinuation From Study) During Double-Blind Treatment, Kaplan-Meier Analysis, Proportional Hazards Model

	Pregabalin (N=108)	Placebo (N=107)	Analysis
Time to response			
Subjects achieving response (n [%])	30 (27.8)	30 (28.0)	
Median follow up time	35.0	35.0	
Time to response (days)			
25th percentile (95% CI)[a]	29.0 (14.0,)	21.0 (6.0,)	
Median (95% CI)[a]			
75th percentile (95% CI)[a]			
Effects			
Treatment			
Hazard ratio (95% CI)			0.874 (0.520, 1.470)
Coefficient (SE)			-0.1342 (0.2651)
p-value			0.6127
Back surgery			
Hazard ratio (95% CI)			1.574 (0.737, 3.362)
Coefficient (SE)			0.4538 (0.3871)
p-value			0.2410
Baseline effect			
Hazard ratio (95% CI)			1.248 (1.041, 1.498)
Coefficient (SE)			0.2219 (0.0929)
p-value			0.0169
Center effect			
p-value[b]			0.6175

Response was defined as a meaningful increase in pain, discontinuation from study for any reason, or initiation of rescue medication for pain due to lumbo-sacral radiculopathy during double-blind treatment. A meaningful increase in pain was defined as a ≥1-point increase in the daily pain rating scale score from randomization; to ensure that the 1-point change was clinically meaningful, subjects must also have had a mean weekly pain score at the end of double-blind treatment that had returned to within 30% of the weekly mean pain score at the start of the study. Follow-up time was the number of days subjects were followed in the study. The median time and 25th and 75th percentiles in time to response and their 95% CIs were obtained from independent Kaplan-Meier analyses. Statistics were obtained from a Cox model with effects for each pooled study center, treatment, back surgery, and baseline daily pain score.
Two Subjects in the pregabalin treatment group did not have any post-baseline pain records and were therefore excluded.
CI=confidence interval; ITT=intent-to-treat; N=the number of ITT subjects in a treatment group; n=number of subjects meeting criteria; SE=standard error
a. The median (and 75th percentile in) time to response were not estimable because < 50% (and 75%) of subjects achieved response. In some instances, the lower and/or upper limits of the 95% CI were not estimable.
b. Centers having <4 randomized and treated subjects were pooled into 1 center.

Secondary efficacy results:

Within the group of all 356 subjects who were treated with single-blind pregabalin and who had mean single-blind baseline and post-baseline pain data, the response rate was 57.9%. Within the group of 218 subjects who completed 4 weeks of single-blind pregabalin treatment and had mean single-blind baseline and end-of-phase pain data, 87.2% of subjects were responders. The response rates were not very different within the subgroups of subjects with and without prior back surgery. Table 3 shows 30% Response Rates during single-blind pregabalin treatment.

Table 3. 30% Response Rates During Single-Blind Pregabalin Treatment

	Subjects Treated With Single-Blind Pregabalin					
	Last Observation			Completers		
	N[a]	n	(%)	N[a]	n	(%)
All subjects	356	206	(57.9)	218	190	87.2
Without prior back surgery	270	160	(59.3)	173	148	85.5
With prior back surgery	86	46	(53.5)	45	42	93.3

Last observation is the last observation during the single-blind period for anyone who received single-blind treatment.
Completers are subjects who did not discontinue during the single-blind treatment period.
Note: Only subjects with a non-missing mean single-blind pregabalin baseline pain score are being analyzed. If no medical history data are available for a subject, then the subject is considered to have no prior back surgery. Subjects with no end of study disposition status in the single-blind period were considered to be completers.
n=number of subjects who responded (≥30% decrease from baseline in mean weekly pain score).
a. number of subjects with mean baseline and post-baseline pain scores.

Post-hoc analyses of pain data collected during the single-blind treatment phase indicated that among all subjects treated with pregabalin, the mean change in pain scores from the start of the placebo run-in (Day 0) to the end of the single-blind pregabalin treatment phase was -2.3.

Subjects reported severe pain on nearly 50% of the days during the screening phase and the placebo run-in phase. That figure decreased to 24.1% during the single-blind treatment phase, and decreased further during the double-blind treatment phase (to 7.1% and 6.4% for pregabalin- and placebo-treated subjects, respectively; Table 4)

Table 4. Number of Days of Mild, Moderate, and Severe Pain by Treatment Period

	Pain Severity			
	None (0)	**Mild (>0, <4)**	**Moderate (≥4, <7)**	**Severe (≥7)**
Screening (All subjects: N=371)				
n[a]	3	77	283	272
Mean (SD) % days in category	0.1 (1.1)	4.5 (11.5)	47.8 (37.6)	47.6 (40.1)
Median (range) % days in category	0.0 (0.0, 14.3)	0.0 (0.0, 100.0)	50.0 (0.0, 100.0)	42.9 (0.0, 100.0)
Placebo run-in (All subjects: N=371)				
n[a]	4	81	272	249
Mean (SD) % days in category	0.3 (4.4)	8.3 (19.7)	45.8 (37.7)	45.5 (41.1)
Median (range)	0.00 (0.0, 80.0)	0.0 (0.0, 100.0)	42.9 (0.0, 100.0)	42.9 (0.0, 100.0)
Single-blind pregabalin treatment (All Subjects: N=356)				
n[a]	48	229	326	228
Mean (SD) % days in category	2.9 (10.8)	29.7 (31.6)	43.3 (29.5)	24.1 (30.7)
Median (range)	0.0 (0.0, 100.0)	18.2 (0.0, 100.0)	40.7 (0.0, 100.0)	10.0 (0.0, 100.0)
Double-blind treatment (All subjects: N=215)				
Pregabalin (N=108)				
n[a]	28	89	85	34
Mean (SD) % days in category	7.3 (17.0)	54.6 (36.8)	31.1 (33.1)	7.1 (18.3)
Median (range)	0.0 (0.0, 93.3)	60.0 (0.0, 100.0)	14.8 (0.0, 100.0)	0.0 (0.0, 100.0)
Placebo (N=107)				
n[a]	34	91	81	33
Mean (SD) % days in category	13.0 (26.6)	49.5 (35.8)	31.2 (33.5)	6.4 (14.9)
Median (range)	0.0 (0.0, 100.0)	0.0 (0.0, 100.0)	18.4 (0.0, 100.0)	0.0 (0.0, 81.5)

Two subjects had no post-randomization pain records and were excluded from the double-blind treatment summary

N=number of randomized subjects; n=number of subjects in each category; SD=standard deviation.

a. indicates number of subjects having at least 1 day of pain in the category. Except for n[a], all statistics were calculated based on the total number of subjects in a group. In this table, 0 days was assigned per category to subjects without any record with pain in that category.

Results of analyses of secondary efficacy data from the double-blind treatment period were consistent with the primary efficacy outcome. No significant differences in favor of pregabalin were observed in the changes from baseline (randomization) to endpoint (LOCF) in the mean weekly pain score or mean weekly sleep interference scale score, and no significant difference between treatments was seen in the distribution of PGIC scores at endpoint (LOCF). An inconsistent effect on measures of anxiety was observed: No significant difference in favor of pregabalin was observed in GA-VAS change scores, but

significantly greater improvement from baseline was observed in the HADS Anxiety score. Significantly greater improvement from baseline was also observed in the HADS Depression score in the pregabalin treatment group compared with the placebo treatment group.

Data are summarized for mean weekly pain score, mean weekly sleep interference scale, HADS Anxiety and Depression scores, GA-VAS scores and PGIC in Table 5, Table 6, Table 7, Table 8, and Table 9, respectively.

Table 5. Changes From Baseline in the Mean Weekly Pain Score During Double-Blind Treatment-ITT Population

	Pregabalin (N=110)	Placebo (N=107)	Analysis Pregabalin vs Placebo
Baseline randomization			
N[a]	108	107	
LS mean (SE)	3.07 (0.16)	2.68 (0.16)	
LS mean (SE) difference			0.39 (0.21)
95% CI			(-0.02, 0.79)
p-value			0.0615
DB endpoint (LOCF)			
N[a]	108	107	
LS mean (SE) change	-0.16 (0.16)	0.05 (0.16)	
LS mean (SE) difference			-0.21 (0.21)
95% CI			(-0.63, 0.21)
p-value			0.3320

LS means are from the ANCOVA model with main effects of treatment and pooled study center and baseline as a covariate, except for the baseline analysis. The double-blind baseline value is the mean weekly pain score based on scores from the 6 days prior to and including the day of randomization. Double-blind baseline statistics were calculated only for subjects who had non-missing change from double-blind baseline to endpoint. Centers with <4 randomized and treated subjects were pooled into 1 center. Note: Two ITT subjects were excluded from the pain analysis because they had no available post-randomization pain records.
ANCOVA=analysis of covariance; CI=confidence interval; DB=double-blind; ITT=intent-to-treat, LOCF=last observation carried forward; LS=least squares; N=number of ITT subjects in each treatment group; SE=standard error; vs=versus.
a. number of subjects with data for analysis.

Table 6. Changes From Baseline in Weekly Sleep Interference Scale Scores During Double-Blind Treatment-ITT Population

	Pregabalin (N=110)	Placebo (N=107)	Analysis Pregabalin vs Placebo
Baseline (randomization)			
N[a]	107	107	
LS mean (SE)	1.45 (0.16)	1.51 (0.16)	
LS mean (SE) difference			-0.06 (0.20)
95% CI			-0.46, 0.34
p-value			0.7694
DB endpoint (LOCF)			
N[a]	107	107	
LS mean (SE) change	0.01 (0.15)	0.20 (0.14)	
LS mean (SE) difference			-0.19 (0.19)
95% CI			-0.56, 0.19
p-value			0.3256

LS means are from the ANCOVA model with main effects of treatment and pooled study center and baseline as a covariate, except for the baseline analysis. Baseline is the mean weekly sleep interference score based on scores from the 6 days prior to and including the day of randomization. Baseline statistics were calculated only for subjects who had non-missing change from baseline to endpoint. Centers with <4 randomized and treated subjects were pooled into 1 center.
Note: Three ITT subjects were excluded from the sleep analysis because they had no available post-randomization sleep records.
ANCOVA=analysis of covariance; CI=confidence interval; DB=double-blind; ITT=intent-to-treat; LOCF=last observation carried forward; LS=least squares; N=number of ITT subjects in each treatment group; SE=standard error; vs=versus
a. number of subjects with data for analysis.

Table 7. Changes From Baseline to Endpoint (LOCF) in the HADS Anxiety and Depression Scale Scores During Double-Blind Treatment-ITT Population

	Pregabalin (N=110)	Placebo (N=107)	Analysis Pregabalin vs Placebo
HADS anxiety			
Baseline (randomization)			
N[a]	100	101	
LS mean (SE)	5.08 (0.38)	5.30 (0.38)	
LS mean (SE) difference			-0.22 (0.49)
95% CI			-1.18, 0.74
p-value			0.6482
DB endpoint (LOCF)			
N[a]	100	101	
LS mean (SE) change	-0.19 (0.30)	0.82 (0.30)	
LS mean (SE) difference			-1.01 (0.39)
95% CI			-1.78, -0.24
p-value			0.0105
HADS depression			
Baseline (randomization)			
N[a]	100	101	
LS mean (SE) change	4.43 (0.38)	4.21 (0.37)	
LS mean (SE) difference			0.22 (0.48)
95% CI			-0.73, 1.17
p-value			0.6475
DB endpoint (LOCF)			
N[a]	100	101	
LS mean (SE) change	-0.57 (0.25)	0.56 (0.25)	
LS mean (SE) difference			-1.12 (0.32)
95% CI			-1.76, -0.49
p-value			0.0006

LS means are from the ANCOVA model with main effects of treatment and pooled study center and baseline as a covariate, except for the baseline analysis. Baseline is the mean weekly pain score based on scores from the 6 days prior to and including the day of randomization. Baseline statistics were calculated only for subjects who had non-missing change from baseline to endpoint. Centers with <4 randomized and treated subjects were pooled into 1 center.

ANCOVA=analysis of covariance; CI=confidence interval; DB=double-blind; HADS= Hospital Anxiety and Depression Scale; ITT=intent-to-treat; LOCF=last observation carried forward; LS=least squares; N=number of ITT subjects in each treatment group; SE=standard error; vs=versus

a. number of subjects with data for analysis

Table 8. Changes From Baseline to Endpoint (LOCF) in GA-VAS Scores During Double-Blind Treatment-ITT Population

	Pregabalin (N=110)	Placebo (N=107)	Analysis Pregabalin vs Placebo
Baseline			
N[a]	96	95	
LS mean (SE)	19.65 (2.37)	17.31 (2.38)	
LS mean (SE) difference			2.33 (3.04)
95% CI			-3.67, 8.34
p-value			0.4440
DB endpoint (LOCF)			
N[a]	96	95	
LS mean (SE) change	1.37 (2.14)	5.66 (2.14)	
LS mean (SE) difference			-4.29 (2.74)
95% CI			-9.70, 1.12
p-value			0.1192

LS means are from the ANCOVA model with main effects of treatment and pooled study center and baseline as a covariate, except for the baseline analysis. Baseline was the day of randomization. Baseline statistics were calculated only for subjects who had non-missing change from baseline to endpoint. Centers with <4 randomized and treated subjects were pooled into one center.
ANCOVA=analysis of covariance; DB=double-blind, CI=confidence interval, GA-VAS=generalized anxiety visual analog scale; ITT=intent-to-treat, LOCF=last observation carried forward; LS=least squares, N=number of ITT subjects in each treatment group; SE=standard error
a. number of subjects with data for analysis.

Table 9. PGIC at Endpoint of the Double-Blind Treatment Period-ITT Population

PGIC at DB endpoint (LOCF)	Pregabalin (N=110)	Placebo (N=107)	Analysis Pregabalin vs Placebo
Very much improved (n [%])	26 (25.7)	33 (33.0)	
Much improved (n [%])	46 (45.5)	34 (34.0)	
Minimally improved (n [%])	24 (23.8)	24 (24.0)	
No change (n [%])	4 (4.0)	5 (5.0)	
Minimally worse (n [%])	1 (1.0)	0	
Much worse (n [%])	0	4 (4.0)	
N assessed (n [%])	101 (91.8)	100 (93.5)	
p-value			0.2164

CMH test for difference; p-values were adjusted for pooled study center at each visit. Centers with <4 randomized and treated subjects were pooled into 1 center.
CMH=Cochran-Mantel-Haenszel; DB=double blind; ITT=intent-to-treat; LOCF=last observation carried forward; N=number of subjects in a treatment group; n=number of subjects with PGIC rating; PGIC=Patient Global Impression of Change; vs=versus

Double-blind treatment with pregabalin did not result in significantly improved scores at endpoint (LOCF) in any of the subject-reported health outcomes measure, including the MOS, PTSS, modified RDQ, WPAI, and EQ-5D. Data for MOS, PTSS, modified RDQ, WPAI, and EQ-5D are summarized in Table 10, Table 11, Table 12, Table 13 and Table 14, respectively.

Table 10. Changes From Baseline to Endpoint (LOCF) in MOS Subscale Scores During Double-Blind Treatment–ITT Population

	Pregabalin (N=110)	Placebo (N=107)	Analysis Pregabalin vs Placebo
Sleep disturbance			
N[a]	102	97	
Baseline mean (SD)	21.53 (16.38)	22.80 (19.01)	
LS mean (SE) change to EP	2.26 (1.58)	6.86 (1.62)	
LS mean (SE) difference			-4.60 (2.05)
95% CI			-8.64, -0.56
p-value			0.0260
Snoring			
N[a]	98	93	
Baseline mean (SD)	41.22 (33.22)	32.69 (32.68)	
LS mean (SE) change to EP	-0.38 (2.34)	-2.17 (2.37)	
LS mean (SE) difference			1.80 (2.94)
95% CI			-4.02, 7.61
p-value			0.5424
Awaken short of breath or with headache			
N[a]	101	97	
Baseline mean (SD)	12.08 (19.61)	10.31 (16.61)	
LS mean (SE) change to EP	-1.16 (1.60)	1.83 (1.63)	
LS mean (SE) difference			-2.99 (2.07)
95% CI			-7.07, 1.09
p-value			0.1499
Sleep quantity			
N[a]	96	94	
Baseline mean (SD)	7.01 (1.28)	7.04 (1.14)	
LS mean (SE) change to EP	0.00 (0.11)	-0.43 (0.12)	
LS mean (SE) difference			0.43 (0.15)
95% CI			0.14, 0.72
p-value			0.0039
Optimal sleep			
N[a]	96	94	
Baseline n (%) optimal	58 (60.4)	55 (58.5)	
Endpoint n (%) optimal	59 (61.5)	54 (57.4)	
Odds ratio			0.848
95% CI			0.443, 1.626
p-value			0.620
Sleep adequacy			
N[a]	102	97	
Baseline mean (SD)	70.10 (23.27)	65.77 (25.12)	
LS mean (SE) change to EP	-1.85 (2.19)	-4.83 (2.25)	
LS mean (SE) difference			2.98 (2.84)
95% CI			-2.62, 8.58
p-value			0.2946
Somnolence			
N[a]	99	97	
Baseline mean (SD)	31.04 (22.07)	30.03 (19.82)	
LS mean (SE) change to EP	-0.89 (1.65)	-2.57 (1.66)	
LS mean (SE) difference			1.68 (2.09)
95% CI			-2.45, 5.81
p-value			0.4225

Table 10. Changes From Baseline to Endpoint (LOCF) in MOS Subscale Scores During Double-Blind Treatment–ITT Population

	Pregabalin (N=110)	Placebo (N=107)	Analysis Pregabalin vs Placebo
9-Item sleep problems index			
N[a]	98	97	
Baseline mean (SD)	24.46 (12.97)	25.53 (14.95)	
LS mean (SE) change to EP	1.02 (1.27)	3.74 (1.27)	
LS mean (SE) difference			-2.72 (1.61)
95% CI			-5.90, 0.47
p-value			0.0937

LS means were from the ANCOVA model with main effects of treatment and pooled study center and baseline as a covariate, except for the baseline analysis. Baseline was defined as the day of randomization. Baseline statistics were calculated only for subjects who had non-missing change from baseline to endpoint. Centers with <4 randomized and treated subjects were pooled into 1 center.
For the optimal sleep analysis, the odds ratio and its 95% CI were calculated by exponentiating the log odds ratio and 95% CI that correspond to the treatment contrast in the logistic regression model. The model for baseline assessment has 1 term for treatment. At endpoint, the model contains a term for baseline. Center has not been included as a covariate in the model because all centers did not have both levels of optimal sleep.
ANCOVA=analysis of covariance; CI=confidence interval; EP=endpoint; ITT=intent-to-treat; LOCF=last observation carried forward; LS=least squares; MOS=Medical Outcomes Study; N=number of ITT subjects in each treatment group; SD=standard deviation; SE=standard error; vs=versus
a. number of subjects with data for analysis.

Table 11. Changes From Baseline to Endpoint (LOCF) in PTSS During Double-Blind Treatment-ITT Population

PTSS Subscale	Pregabalin (N=110)	Placebo (N=107)	Analysis Pregabalin vs Placebo
Impact of current pain medication			
N[a]	98	98	
Baseline mean (SD)	69.84 (23.49)	72.81 (22.19)	
LS mean (SE) change to EP	-0.84 (2.04)	-1.35 (2.07)	
LS mean (SE) difference			0.51 (2.65)
95% CI			-4.71, 5.74
p-value			0.8471
Satisfaction with current pain medication and care			
N[a]	99	96	
Baseline mean (SD)	77.75 (16.04)	77.86 (14.52)	
LS mean (SE) change to EP	-1.49 (1.72)	-4.36 (1.74)	
LS mean (SE) difference			2.87 (2.21)
95% CI			-1.49, 7.22
p-value			0.1951

LS means were from the ANCOVA model with main effects of treatment and pooled study center and baseline as a covariate, except for the baseline analysis. Baseline was the day of randomization. Baseline statistics were calculated only for subjects who had non-missing change from baseline to endpoint. Centers with <4 randomized and treated subjects were pooled into 1 center.
ANCOVA=analysis of covariance; CI=confidence interval; EP=endpoint; ITT=intent-to-treat ; LOCF=last observation carried forward; LS=least squares; N=number of ITT subjects in each treatment group; PTSS=pain treatment satisfaction scale; SD=standard deviation; SE=standard error; vs=versus
a. number of subjects with data for analysis.

Table 12. Changes From Baseline to Endpoint (LOCF) in Modified RDQ Total Score During Double-Blind Treatment-ITT Population

	Pregabalin (N=110)	Placebo (N=107)	Analysis Pregabalin vs Placebo
N[a]	89	87	
Baseline mean (SD)	10.03 (6.27)	9.95 (6.25)	
LS mean (SE) change to EP	-0.33 (0.46)	0.61 (0.47)	
LS mean (SE) difference			-0.94 (0.60)
95% CI			-2.12, 0.24
p-value			0.1177

LS means were from the ANCOVA model with main effects of treatment and pooled study center and baseline as a covariate, except for the baseline analysis. Baseline was the day of randomization. Baseline statistics were calculated only for subjects who had non-missing change from baseline to endpoint. Centers with <4 randomized and treated subjects were pooled into 1 center.
ANCOVA=analysis of covariance; CI=confidence interval; EP=endpoint; ITT=intent-to-treat; LOCF=last observation carried forward; LS=least squares; N=number of ITT subjects in each treatment group; RDQ=Roland-Morris Disability Questionnaire; SD=standard deviation; SE=standard error; vs=versus
a. number of subjects with data for analysis

Table 13. Changes From Baseline to Endpoint (LOCF) in WPAI Questionnaire During Double-Blind Treatment-ITT Population

	Pregabalin (N=110)	Placebo (N=107)	Analysis Pregabalin vs Placebo
Percent work time missed			
N[a]	29	33	
Baseline mean (SD)	6.75 (24.62)	17.88 (35.72)	
LS mean (SE) change to EP	-3.16 (4.04)	0.81 (3.88)	
LS mean (SE) difference			-3.97 (5.39)
95% CI			-14.87, 6.92
p-value			0.4652
Percent impairment while working			
N[a]	35	43	
Baseline mean (SD)	17.71 (13.74)	24.88 (23.34)	
LS mean (SE) change to EP	-0.18 (3.38)	4.48 (3.03)	
LS mean (SE) difference			-4.66 (4.34)
95% CI			-13.35, 4.03
p-value			0.2873
Percent overall work impairment			
N[a]	28	30	
Baseline mean (SD)	20.93 (19.67)	32.40 (30.46)	
LS mean (SE) change to EP	-0.66 (4.46)	2.60 (4.06)	
LS mean (SE) difference			-3.27 (5.76)
95% CI			-14.95, 8.42
p-value			0.5744
Percent activity impairment			
N[a]	97	97	
Baseline mean (SD)	31.75 (21.65)	30.93 (22.83)	
LS mean (SE) change to EP	-1.73 (2.26)	1.60 (2.17)	
LS mean (SE) difference			-3.33 (2.73)
95% CI			-8.71, 2.06
p-value			0.2241

LS means were from the ANCOVA model with main effects of treatment and pooled study center and baseline as a covariate, except for the baseline analysis. Baseline was the day of randomization. Baseline statistics were calculated only for subjects who had non-missing change from baseline to endpoint. Centers with <4 randomized and treated subjects were pooled into 1 center.
ANCOVA=analysis of covariance; CI=confidence interval; EP=endpoint; ITT=intent-to-treat; LOCF=last observation carried forward; LS=least squares; N=number of ITT subjects in each treatment group; SD=standard deviation; SE=standard error; WPAI=Work Productivity and Activity Impairment
a. number of subjects with data for analysis

Table 14. Summary of EQ-5D Utility Scores by Pain Severity Score-ITT Population

Utility Score (-0.594-1)	Mean Pain Score Category			
	Mild (<4)	Moderate (≥4,<7)	Severe (≥7)	Total (0-10)
Placebo run-in[aError! Reference source not found.]				
N	25	116	70	211
Mean (SD)	0.55 (0.23)	0.49 (0.28)	0.25 (0.37)	0.42 (0.33)
Median (Min, Max)	0.62 (0.06, 0.80)	0.62 (-0.24, 0.88)	0.16 (-0.59, 0.85)	0.59 (-0.59, 0.88)
Single-blind pregabalin[bError! Reference source not found.]				
N	151	62	0	213
Mean (SD)	0.71 (0.17)	0.56 (0.23)		0.67 (0.20)
Median (Min, Max)	0.73 (0.02, 1.00)	0.62 (0.00, 0.80)		0.69 (0.00, 1.00)
Double-blind treatment[cError! Reference source not found.]				
Pregabalin				
N	69	25	4	98
Mean (SD)	0.72 (0.20)	0.45 (0.29)	0.16 (0.29)	0.63 (0.27)
Median (Min, Max)	0.76 (-0.18, 1.00)	0.59 (-0.02, 0.80)	0.04 (-0.02, 0.59)	0.69 (-0.18, 1.00)
Placebo				
N	68	31	2	101
Mean (SD)	0.73 (0.19)	0.47 (0.33)	0.33 (0.42)	0.64 (0.27)
Median (Min, Max)	0.74 (-0.18, 1.00)	0.59 (-0.24, 0.80)	0.33 (0.03, 0.62)	0.73 (-0.24, 1.00)

EQ-5D=Euro Quality of Life; ITT=intent-to-treat; max=maximum; min=minimum; N= number of ITT subjects in each treatment group; SD=standard deviation

a. EQ-5D scores were based on those collected at Day 0 (start of placebo run-in). Pain scores were based on the mean scores collected during the placebo run-in. All scores were based on subjects completing the placebo run-in.

b. EQ-5D scores were based on those collected at Day 35 (randomization). Pain scores were based on the mean scores collected during the single-blind pregabalin treatment period. All scores were based on subjects completing the single-blind pregabalin treatment period.

c. EQ-5D scores were based on those collected at the end of the study. Pain scores were based on the mean scores collected during the double-blind treatment period.

Table 15. Summary of EQ-5D Health State Profile and Visual Analog Scale by Pain Severity Score - ITT Population

VAS Score (0-100)	Mean Pain Score Category			
	Mild (<4)	Moderate (≥4,<7)	Severe (≥7)	Total (0-10)
Placebo run-in[a]				
N	24	114	71	209
Mean (SD)	62.1 (19.5)	52.8 (19.3)	44.3 (21.9)	60.0 (20.9)
Median (Min, Max)	62.5 (20.0, 90.0)	50.5 (1.0, 95.0)	48.0 (0.0, 90.0)	50.0 (0.0, 95.0)
Single-blind pregabalin[b]				
N	152	62	0	214
Mean (SD)	73.0 (18.2)	56.6 (15.8)		68.3 (19.1)
Median (Min, Max)	75.0 (19.0, 100.0)	55.5 (25.0, 90.0)		70.0 (19.0, 100.0)
Double-blind treatment[c]				
Pregabalin				
N	69	24	3	96
Mean (SD)	75.4 (16.0)	60.8 (22.2)	58.3 (16.1)	71.2 (18.8)
Median (Min, Max)	78.0 (16.0, 99.0)	59.0 (21.0, 95.0)	65.0 (40.0, 70.0)	72.5 (16.0, 99.0)
Placebo				
N	68	30	2	100
Mean (SD)	74.7 (20.8)	58.1 (17.7)	20.5 (13.44)	68.7 (22.2)
Median (Min, Max)	80.0 (7.0, 100.0)	59.5 (25.0, 95.0)	20.5 (11.0, 30.0)	72.0 (7.0, 100.0)

EQ-5D=Euro Quality of Life; ITT=intent-to-treat; max=maximum; min=minimum; N=number of ITT subjects in each treatment group; SD=standard deviation

a. EQ-5D scores were based on those collected at Day 0 (start of placebo run-in). Pain scores were based on the mean scores collected during the placebo run-in. All scores were based on subjects completing the placebo run-in.

b. EQ-5D scores were based on those collected at Day 35 (randomization). Pain scores were based on the mean scores collected during the single-blind pregabalin treatment period. All scores were based on subjects completing the single-blind pregabalin treatment period.

c. EQ-5D scores were based on those collected at the end of the study. Pain scores were based on the mean scores collected during the double-blind treatment period.

On the Lumbar Radiculopathy Pain Management questionnaire, at randomization the investigators recommended invasive treatment for 36 (19.9%) pregabalin responders and 13 (43.3%) pregabalin non-responders. At the end of the study, the investigators recommended invasive surgery for 28 (28.6%) pregabalin completers and 15 (17.4%) placebo completers. Data at randomization and the end of study are summarized in Table 16 and Table 17 respectively.

Table 16. Lumbar Radiculopathy Pain Management Questionnaire at Randomization-Pregabalin Responders and Non-Responders

Clinician Recommended[a]	Pregabalin Responders[b]			Pregabalin Non-Responders[b]		
	All Subjects (N=181) n (%)	Back Surgery		All Subjects (N=30) n (%)	Back surgery	
		Yes (N=41) n (%)	No (N=140) n (%)		Yes (N=3) n (%)	No (N=27) n (%)
Non-invasive						
Medication	180 (99.5)	41 (100.0)	139 (99.3)	30 (100.0)	3 (100.0)	27 (100.0)
Psychotherapy	27 (14.9)	11 (26.8)	16 (11.4)	7 (23.3)	0	7 (25.9)
Physical therapy	148 (81.8)	36 (87.8)	112 (80.0)	22 (73.3)	2 (66.7)	20 (74.1)
Any non-invasive	180 (99.5)	41 (100.0)	139 (99.3)	30 (100.0)	3 (100.0)	27 (100.0)
Invasive						
Spinal or related nerves block	31 (17.1)	8 (19.5)	23 (16.4)	9 (30.0)	1 (33.3)	8 (29.6)
Spinal cord stimulator	7 (3.9)	3 (7.3)	4 (2.9)	4 (13.3)	1 (33.3)	3 (11.1)
Surgery	2 (1.1)	1 (2.4)	1 (0.7)	2 (6.7)	0	2 (7.4)
Any invasive	36 (19.9)	11 (26.8)	25 (17.9)	13 (43.3)	2 (66.7)	11 (40.7)

Only treated subjects with pain management records and medical history data were included. More than 1 invasive or non-invasive procedure could have been recommended for a subject
N=number of intent-to-treat subjects in each treatment group; n= number of subjects meeting criteria
a. Procedure probably or strongly recommended by the clinician.
b. Pregabalin responders were subjects who had a decrease in mean weekly pain of at least 30% at the end of single-blind pregabalin treatment; 23 subjects who were randomized (11%) did not meet this criteria.

Table 17. Lumbar Radiculopathy Pain Management Questionnaire at End of Study-Pregabalin and Placebo Completers

Clinician Recommended[a]	Pregabalin Completers[b]			Placebo Completers[b]		
	All Subjects (N=98) n (%)	Back Surgery		All Subjects (N=86) n (%)	Back Surgery	
		Yes (N=23) n (%)	No (N=75) n (%)		Yes (N=16) n (%)	No (N=70) n (%)
Non-invasive						
Medication	95 (96.9)	23 (100.0)	72 (96.0)	81 (94.2)	16 (100.0)	65 (92.9)
Psychotherapy	19 (19.4)	8 (34.8)	11 (14.7)	13 (15.1)	6 (37.5)	7 (10.0)
Physical therapy	72 (73.5)	16 (69.6)	56 (74.7)	63 (73.3)	16 (100.0)	47 (67.1)
Any non-invasive	97 (99.0)	23 (100.0)	74 (98.7)	82 (95.4)	16 (100.0)	66 (94.3)
Invasive						
Spinal or related nerves block	22 (22.5)	5 (21.7)	17 (22.7)	13 (15.1)	2 (12.5)	11 (15.7)
Spinal cord stimulator	6 (6.1)	3 (13.0)	3 (4.0)	3 (3.5)	1 (6.3)	2 (2.9)
Surgery	3 (3.1)	1 (4.4)	2 (2.7)	2 (2.3)	0 (0.0)	2 (2.9)
Any invasive	28 (28.6)	9 (39.1)	19 (25.3)	15 (17.4)	3 (18.8)	12 (17.1)

Only treated subjects with pain management records and medical history data were included. The last record per subject after randomization was used for analysis. More than 1 invasive or non-invasive procedure could have been recommended for a subject.
N=number of intent-to-treat subjects in each treatment group; n=number of subjects in each category
a. Procedure probably or strongly recommended by the clinician.
b. Subjects who were randomized to pregabalin or placebo, respectively, and completed the study.

Safety Results: During treatment with pregabalin over the course of the entire study, including the taper period, 298 (81.9%) subjects experienced a total of 830 treatment-emergent AEs. Most frequently reported treatment-related and all-causality treatment-emergent AEs are presented in Table 18 and Table 19, respectively.

Table 18. Treatment-Related Treatment-Emergent AEs by Severity and Treatment Phase That Occurred in ≥2% of Subjects During Pregabalin Treatment Overall–Safety Subjects

Adverse event (MedDRA SOC/preferred term)	Single-Blind Pregabalin[a] (N=364)	Double Blinded Treatment Phase[b]		All Pregabalin[c] (N=364)
		Pregabalin (N=110)	Placebo (N=107)	
	n (%)	n (%)	n (%)	n (%)
Ear and labyrinth				
Vertigo	28 (7.7)	0	0	28 (7.7)
Eye disorders				
Vision blurred	8 (2.2)	2 (1.8)	0	10 (2.7)
Gastrointestinal				
Dry mouth	30 (8.2)	1 (0.9)	1 (0.9)	31 (8.5)
Constipation	25 (6.9)	1 (0.9)	0	25 (6.9)
Nausea	12 (3.3)	0	3 (2.8)	12 (3.3)
General disorders				
Fatigue	30 (8.2)	0	1 (0.9)	31 (8.5)
Edema peripheral	11 (3.0)	3 (2.7)	1 (0.9)	14 (3.8)
Investigations				
Weight increased	19 (5.2)	3 (2.7)	2 (1.9)	24 (6.6)
Metabolism & nutrition				
Increased appetite	11 (3.0)	0	0	11 (3.0)
Nervous system				
Dizziness	106 (29.1)	4 (3.6)	2 (1.9)	109 (29.9)
Somnolence	44 (12.1)	1 (0.9)	1 (0.9)	45 (12.4)
Headache	18 (4.9)	1 (0.9)	2 (1.9)	19 (5.2)
Balance disorder	10 (2.7)	1 (0.9)	0	10 (2.7)
Disturbance in attention	10 (2.7)	1 (0.9)	0	11 (3.0)
Depressed level of consciousness	10 (2.7)	0	0	10 (2.7)

AE=adverse event; MedDRA=medical dictionary and regulatory affairs; N=number of randomized subjects; n=number of subjects experienced adverse events; SOC=system organ class

a. Includes TEAEs that began or worsened in severity during the single-bind period (4 weeks) or during the subsequent 1-week pregabalin taper for subjects who were not randomized. For subjects randomized to placebo, does not include TEAEs that began or worsened in severity during the 1-week pregabalin taper that followed the single-blind pregabalin taper and preceded the start of double-blind placebo treatment.

b. Includes TEAEs that began or worsened in severity during the double-blind period (5 weeks) or during the 1-week taper that followed the double-blind period for all randomized subjects. For subjects randomized to placebo, includes TEAEs that began or worsened in severity during the 1-week pregabalin taper that followed the single-blind period and preceded the start of double-blind placebo treatment.

c. Includes TEAEs that began or worsened in severity at any time during treatment with pregabalin (up to 10 weeks).

Table 19. Treatment-Emergent AEs (All Causalities) That Occurred in ≥2% of Subjects During the Single-Blind Pregabalin Treatment, Double-Blind Treatment, and/or Pregabalin Treatment Overall–Safety-Evaluable Subjects

Adverse Event (MedDRA SOC/Preferred term)	Single-Blind Pregabalin[a] (N=364)	Double Blinded Treatment Phase[b]		All Pregabalin[c] (N=364)
		Pregabalin (N=110)	Placebo (N=107)	
	n (%)	n (%)	n (%)	n (%)
Ear and labyrinth disorders				
Vertigo	28 (7.7)	0	0	28 (7.7)
Eye disorders				
Vision blurred	8 (2.2)	3 (2.7)	0	11 (3.0)
Gastrointestinal disorders				
Dry mouth	31 (8.5)	1 (0.9)	1 (0.9)	32 (8.8)
Constipation	28 (7.7)	1 (0.9)	0	28 (7.7)
Nausea	12 (3.3)	1 (0.9)	4 (3.7)	13 (3.6)
Diarrhea	9 (2.5)	1 (0.9)	0	10 (2.7)
General disorders				
Fatigue	32 (8.8)	0	2 (1.9)	33 (9.1)
Edema peripheral	15 (4.1)	5 (4.5)	2 (1.9)	19 (5.2)
Infections and infestations				
Nasopharyngitis	13 (3.6)	5 (4.5)	4 (3.7)	18 (4.9)
Influenza	5 (1.4)	4 (3.6)	0	9 (2.5)
Investigations				
Weight increased	20 (5.5)	3 (2.7)	2 (1.9)	25 (6.9)
Metabolism and nutrition				
Increased appetite	11 (3.0)	0	0	11 (3.0)
Musculoskeletal				
Back pain	5 (1.4)	6 (5.5)	2 (1.9)	12 (3.3)
Pain in extremity	9 (2.5)	3 (2.7)	3 (2.8)	11 (3.0)
Muscle spasms	8 (2.2)	1 (0.9)	1 (0.9)	9 (2.5)
Arthralgia	6 (1.6)	3 (2.7)	1 (0.9)	8 (2.2)
Nervous system				
Dizziness	108 (29.7)	4 (3.6)	2 (1.9)	111 (30.5)
Somnolence	45 (12.4)	1 (0.9)	1 (0.9)	46 (12.6)
Headache	24 (6.6)	1 (0.9)	4 (3.7)	26 (7.1)
Balance disorder	10 (2.7)	1 (0.9)	0	10 (2.7)
Depressed level of consciousness	10 (2.7)	0	0	10 (2.7)
Disturbance in attention	10 (2.7)	1 (0.9)	0	11 (3.0)

AE=adverse event; MedDRA=medical dictionary and regulatory affairs, N=number of randomized subjects; n=number of subjects experienced adverse event; SOC=system organ class

a. Includes TEAEs that began or worsened in severity during the single-blind period or the subsequent 1-week pregabalin taper for subjects who were not randomized.

b. Includes TEAEs that began or worsened in severity during the double-blind period or the subsequent 1-week taper. For subjects randomized to placebo, includes TEAEs that began or worsened in severity during the 1-week pregabalin taper that followed the single-blind period.

c. Includes TEAEs that began or worsened in severity at any time during treatment with pregabalin (up to 10 weeks).

Over the course of the study, 36 (9.9%) subjects permanently discontinued treatment due to treatment-emergent AEs that started during treatment with pregabalin. Most subjects who permanently discontinued pregabalin treatment (32 of the 36 subjects) did so due to AEs that started during the initial 4-week single-blind pregabalin treatment period. The other 4 subjects included 2 subjects who discontinued due to AEs that began during double-blind pregabalin treatment and 2 subjects who discontinued during the first week of double-blind placebo treatment, during which subjects were being tapered off pregabalin. Four additional subjects discontinued due to AEs that started during double-blind placebo treatment (for a total of 6 subjects who discontinued during the double-blind placebo treatment period). The 4 subjects included 1 subject who also discontinued due to AEs that began during single-blind pregabalin treatment. Details of discontinuations are provided in Table 20.

Table 20. Subjects who Discontinued Treatment due to Treatment-Emergent AEs-Safety-Evaluable Subjects

Subject Serial Number	Adverse Event MedDRA Preferred Term	Treatment Related[a]?	Serious?	Intensity[a]
1	Eyelid edema	Yes	No	Moderate
2	Dizziness	Yes	No	Moderate
3	Face edema	Yes	No	Mild
	Peripheral edema	Yes	No	Mild
4	Balance disorder	Yes	No	Moderate
	Confusional state	Yes	No	Mild
5	Balance disorder	Yes	No	Moderate
	Tunnel vision	Yes	No	Moderate
6	Apathy	Yes	No	Severe
7	Dizziness	Yes	No	Severe
8	Vision blurred	Yes	No	Mild
	Dizziness	Yes	No	Mild
9	Cholangitis	Yes	No	Moderate
10	Periorbital edema	Yes	No	Mild
11	Depressed level of consciousness	Yes	No	Severe
	Dizziness	Yes	No	Severe
12	Asthenia	Yes	No	Severe
	Pain	Yes	No	Severe
	Somnolence	Yes	No	Moderate
13	Vertigo	Yes	No	Severe
	Dizziness	Yes	No	Severe
	Disorientation	Yes	No	Severe
14	Dizziness	Yes	No	Severe
	Somnolence	Yes	No	Severe
15	Diarrhea	Yes	No	Mild
	Vomiting	Yes	No	Mild
	Rash	Yes	No	Mild
16	Dry mouth	Yes	No	Moderate
	Depressed level consciousness	Yes	No	Severe
	Dizziness	Yes	No	Severe
17	Arthropathy	Yes	No	Moderate
18	Neuralgia	No	Yes	Moderate
19	Tendonitis	No	No	Moderate
20	Dry mouth	Yes	No	Mild
	Gastritis	Yes	No	Moderate
	Disturbance in attention	Yes	No	Mild
21	Stupor	Yes	No	Severe
22	Sexual dysfunction	Yes	No	Moderate
23	Headache	Yes	No	Moderate
24	Mydriasis	Yes	No	Severe
	Feeling drunk	Yes	No	Severe
25	Dizziness	Yes	No	Moderate
26	Somnolence	Yes	No	Moderate
27	Gastritis	No	No	Mild
28	Arthropathy	No	No	Moderate
	Back pain	No	No	Moderate
	Pain in extremity	No	No	Moderate
29	Vertigo	Yes	No	Moderate
30	Dizziness	Yes	No	Mild
	Tremor	Yes	No	Mild

Table 20. Subjects who Discontinued Treatment due to Treatment-Emergent AEs-Safety-Evaluable Subjects

Subject Serial Number	Adverse Event MedDRA Preferred Term	Treatment Related[a]?	Serious?	Intensity[a]
31	Vertigo	Yes	No	Mild
	Fatigue	Yes	No	Moderate
	Feeling drunk	Yes	No	Mild
	Gait disturbance	Yes	No	Mild
	Weight increased	Yes	No	Mild
	Disturbance in attention	Yes	No	Moderate
	Paresthesia	Yes	No	Mild
	Disorientation	Yes	No	Moderate
32	Fatigue	Yes	No	Moderate
Double-blind fixed-dose pregabalin				
33	Abdominal pain upper	Yes	No	Moderate
34	Abdominal pain upper	No	No	Moderate
	Genitourinary tract infection	No	No	Moderate
Double-blind placebo				
19[b]	Myalgia	No	No	Mild
35[c]	Jaundice	No	Yes	Moderate
36[c]	Radiculitis lumbo-sacral	No	No	Severe
37	Pain	Yes	No	Severe
38	Tachycardia	Yes	No	Moderate
39	Gastric bypass	No	No	Severe

Start/stop days of the treatment phase in which the AE emerged
MedDRA, Medical Dictionary for Regulatory Activities, version 10.0.
AE=adverse event; MedDRA=Medical Dictionary for Regulatory Activities
a. In the judgment of the investigator.
b. Subject discontinued due to AEs that emerged during the single-blind pregabalin period (tendonitis) and double-blind placebo period (myalgia).
c. Subject discontinued due to AEs that emerged during the 1-week taper at the start of the double-blind placebo period.

The most common treatment-emergent AE (all causalities) leading to permanent discontinuation of pregabalin treatment was dizziness (9 subjects), followed by somnolence and vertigo (3 subjects for each event), and arthropathy, gastritis, dry mouth, fatigue, balance disorder, feeling drunk, disturbance in attention, depressed level of consciousness, and disorientation (each event in 2 subjects). All other events occurred in 1 subject each. (Note that 2 subjects discontinued due to edema, 1 due to eyelid edema and 1 due to face edema and peripheral edema). In all but 7 subjects, the AEs that led to treatment discontinuation were considered related to treatment.

Nine (2.5%) subjects discontinued pregabalin treatment due to treatment-emergent AEs that were considered severe. These discontinuations occurred during the single-blind pregabalin treatment period. The most common severe AE leading to discontinuation of pregabalin treatment was dizziness (5 subjects), followed by disturbance in attention (2 subjects), and feeling drunk, mydriasis, apathy, stupor, asthenia, gait disturbance, somnolence, vertigo, and disorientation (each event in 1 subject). All severe AEs leading to permanent discontinuation of pregabalin were considered related to treatment.

Three (2.8%) subjects discontinued due to severe AEs during the double-blind placebo treatment period: 2 subjects due to radiculitis and pain during the pregabalin taper and 1 subject due to gastric bypass.

No subjects dies during the study. Six subjects experienced SAEs during the active treatment phases of the study (ie, after the placebo run-in phase) as summarized in Table 21.

Table 21. Serious Adverse Events (All Causalities and Treatment Related)

	Single-Blind Pregabalin[a] (N=364)	Double-blind Treatment[b]		All Pregabalin[c] (N=364)
		Pregabalin (N=110)	Placebo (N=107)	
AE parameter (incidence):	n (%)	n (%)	n (%)	n (%)
Non-fatal SAEs (all causalities)	4 (1.1)	2 (1.8)	0	6 (1.6)
Diarrhea	1 (0.3)	0	0	1 (0.3)
Cellulitis	1 (0.3)	0	0	1 (0.3)
Neuralgia	1 (0.3)	0	0	1 (0.3)
Ovarian cyst	1 (0.3)	0	0	1 (0.3)
Jaundice	0	1	0	1 (0.3)
Ankle fracture	0	1	0	1 (0.3)
Non-fatal SAEs (treatment-related)	0	0	0	0

Two additional subjects experienced non-fatal SAEs before the start of active treatment (cholelithiasis and contusion)
AE=adverse event; N=number of randomized subjects; n=number of subjects meeting criteria; SAE=serious adverse event; TEAE=treatment-emergent adverse events
a. Includes TEAEs that began or worsened in severity during single-blind period or pregabalin taper for subjects who were not randomized.
b. Includes TEAEs that began or worsened in severity during the double-blind period or the taper. For subjects randomized to placebo, includes TEAEs that began or worsened in severity during the 1-week pregabalin taper after the end of single-blind pregabalin.
c. Includes TEAEs that began or worsened in severity at any time during treatment with pregabalin (up to 10 weeks).

The medications most commonly taken prior to study entry were pain medications, including paracetamol, diclofenac, tramadol, and ibuprofen, each of which was taken by more than 20% of subjects. Paracetamol (taken by 21% of subjects) and ibuprofen (14%) were among the most commonly used concomitant pain medications.

Clinical samples were collected for laboratory analysis at screening (baseline) and the final visit only. No notable median changes from baseline were observed. The most common (incidence of ≥2%) clinically significant laboratory test abnormalities were elevations in triglycerides (8%), urine specific gravity (5%) and glucose (3%).

There were no clinically significant findings reported in vital signs.

CONCLUSIONS:

- Among subjects with chronic lumbo-sacral radiculopathy due to spinal stenosis or disk herniation who responded to 4 weeks of treatment with pregabalin 150 to 600 mg/day,

those who were subsequently randomized to double-blind pregabalin were no more or less likely than those who were subsequently randomized to double-blind placebo to experience a meaningful increase in pain over a 5-week period. Approximately 28% of subjects in each group experienced a meaningful increase in pain during double-blind treatment. The 25th percentile in time to a meaningful increase in pain was 29.0 days in the pregabalin treatment group and 21.0 days in the placebo treatment group.

- Results of analyses of secondary efficacy and health outcomes data from the double-blind treatment period were consistent with the primary efficacy results.

- Following 4 weeks of single-blind pregabalin treatment, 87.2% of subjects were responders (experienced a reduction in pain of ≥30%). Among subjects who received at least 1 dose of single-blind pregabalin, the response rate was 57.9%.

- Subjects reported severe pain on nearly 50% of the days during the screening period and the placebo run-in. That figure decreased to 24.1% during the single-blind treatment period and decreased further during the double-blind treatment period (to 7.1% and 6.4% for pregabalin and placebo-treated subjects, respectively).

- Post-hoc analyses of single-blind pain data indicated that among all subjects who entered the study, the mean weekly pain score was reduced by 2.3 points at endpoint from a mean weekly score of 6.37 at baseline, a clinically meaningful reduction. The mean weekly sleep score prior to the start of the placebo run-in was 4.40, and the change in the mean weekly score to the end of the single-blind pregabalin treatment period was-2.14, also clinically meaningful. At the end of single-blind treatment, a majority (>98%) of subjects in both treatment groups with PGIC data rated themselves as improved relative to the start of the study in terms of their overall status.

- Prior back surgery was not demonstrated to have had an impact on subject response during the single-blind or double-blind treatment periods.

- Pregabalin was demonstrated to be safe and well-tolerated in the treatment of subjects with chronic lumbo-sacral radiculopathy due to spinal stenosis or disk herniation. The safety profile of pregabalin in this study was consistent with that reported in the current Lyrica® product label.

- Pregabalin treatment was associated with a mean increase in body weight of 1.3 kg from the beginning to the end of the study. Subjects later randomized to placebo during the double-blind phase lost weight, indicating a possible reversible effect once pregabalin is stopped.