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

PROTOCOL NO. A0081183

PROTOCOL TITLE: Randomized, Double-Blind, 6-Week Study of Pregabalin in Subjects With Restless Legs Syndrome

Study Centers: A total of 24 centers took part in the study and enrolled subjects; 14 in the United States (US), 7 in Germany, 2 in Austria and 1 in Spain.

Study Initiation and Final Completion Dates: 18 April 2008 to 17 January 2009

Phase of Development: Phase 2b

Study Objectives:

Primary Objective: To characterize the dose-response relationship for pregabalin in the treatment of restless legs syndrome (RLS) symptoms in subjects with idiopathic RLS using the International Restless Legs Study Group Rating Scale (IRLS).

Secondary Objectives:

- To assess the tolerability and safety of pregabalin in RLS subjects with respect to dose level.
- To assess the pregabalin dose response of the following endpoints:
  - Clinical Global Impressions-Improvement (CGI-I) responders.
  - Subjective perception of sleep.
  - Quality of life in RLS and.
  - Early study discontinuation due to adverse events (AEs).

METHODS

Study Design: This was a randomized, 6-arm, parallel-group, double-blind, placebo-controlled study to assess the safety, tolerability and efficacy of pregabalin at doses ranging from 50 to 450 mg/day in subjects with moderate to severe, idiopathic RLS.

Subjects who met entrance criteria at Screening began a washout period followed by a 7-day, single-blind, placebo run-in. At the end of the placebo run-in, eligible subjects were randomized to 1 of 6 treatment arms; 5 treatment arms for pregabalin and 1 treatment arm for placebo. The pregabalin dose groups included: 50, 100, 150, 300, and 450 mg/day. The group size was 20 subjects for each arm. Depending on treatment assignment, an upward titration to the assigned dose was required and lasted up to 2 weeks. Thereafter, doses remained fixed for the duration of the study. There was a 1-week taper period following 6 weeks of treatment. The schedule of activities is provided in Table 1.

Table 1. Schedule of Activities

Visit[a]	**1**		**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**[b]
End of Study Week	**-3**	**-2**	**-1**	**0**	**1**	**2**	**4**	**6**	**7**	**8**
Study Day	**-21**	**-14**	**-7**	**1**	**7**	**14**	**28**	**42**	**49**	**56**
Informed consent	X									
Medical history	X									
Physical examination	X							X		
Diagnosis (RLS-SFDQ9, RLS-TDI)	X									
RLS-TDI (diagnosis confirmation via phone)[c]		X								
Vital signs (sitting and standing)	X			X	X	X	X	X	X	
Body weight	X							X		
Laboratory assessment										
Hematology	X							X		
Chemistry	X							X		
Serum Ferritin	X									
Urinalysis	X							X		
Urine Pregnancy Test[d]	X			X				X		
Urine Drug Screen	X			X				X		
ECG	X			X	X	X	X	X	X	
Eligibility	X		X	X						
Randomization				X						
IRLS			X	X	X	X	X	X	X	
CGI-S	X			X	X	X	X	X		
CGI-I					X	X	X	X		
SSQ[e]			X	X	X	X	X	X		
MOS-SS				X	X	X	X	X		
SF36, RLS-QoL				X				X		
PK sampling[f]							X	X		
SenseWear armband sleep monitor			X[g]	X[h]			X[g]	X[h]		
Study drug dispensing			X[i]	X	X	X	X	X		
Prior/concomitant medication	X----------									----------X
Adverse events	X----------									----------X

CGI-I = clinical global impressions-improvement; CGI-S = clinical global impressions-severity; ECG = electrocardiogram; IRB/IEC = Institutional Review Board/Independent Ethics Committee; IRLS = International Restless Legs Study Group Rating Scale; MOS-SS = medical outcomes study-sleep scale; PK = pharmacokinetic; RLS-QoL = restless legs syndrome quality of life questionnaire; RLS-SFDQ9 = Cambridge-Hopkins restless legs syndrome short form diagnostic questionnaire; RLS-TDI = restless legs syndrome-telephone diagnostic interview; SF36 = short form 36; SSQ = subjective sleep questionnaire.

a. The allowed visit window was ±3 days.
b. Optional visit at Investigator's discretion for unresolved issues.
c. Completed 48 hours after approval of Screening tests.
d. Women of childbearing potential only. Could be repeated per request of IRB/IECs or if required by local regulators.
e. SSQ was administered by subjects at home every morning within 30 minutes of waking up. Subjects returned the diary at each clinical visit.
f. A 5 mL blood sample was collected. Information concerning the time when the blood sample was drawn and the time when the last dose was administered was recorded.
g. Dispensed the device. Subject wore the arm band for 3 consecutive nights starting 5 days (nights) prior to the next visit. For replacement, the sponsor was emailed.
h. Collected the device.
i. Single-blind placebo run-in.

Number of Subjects (Planned and Analyzed): One hundred twenty (120) subjects (20 subjects per treatment arm; ie, pregabalin 50 mg, 100 mg, 150 mg, 300 mg, 450 mg, and placebo) were planned to be enrolled into the study. A total of 218 subjects (155 in US, 45 in Germany, 11 in Austria and 7 in Spain) were screened in the study. A total of 137 subjects were randomized to study treatment (23 in placebo; 22 in pregabalin 50 mg; 23 in pregabalin 100 mg; 22 in pregabalin 150 mg; 24 in pregabalin 300 mg; and 23 in pregabalin 450 mg) and analyzed for safety and efficacy.

Diagnosis and Main Criteria for Inclusion: Male and female subjects aged 18 to 65 years with moderate to severe idiopathic RLS, with symptoms occurring predominantly in the evening which interfered with sleep onset or maintenance were included in the study.

Subjects were excluded based on any secondary RLS, requirement for treatment of daytime RLS symptoms and symptomatic neuropathies.

Study Treatment: Study medication was provided as blinded capsules of pregabalin (50, 100, 150, 300 and 450 mg) and matching placebo. Subjects received a single daily oral dose of pregabalin or matching placebo for a total of 7 weeks (6 weeks of treatment followed by a 1-week taper).

During the first 2 weeks of the double-blind treatment period (Weeks 1 and 2), subjects assigned to pregabalin doses of 100 mg/day or higher had their doses escalated according to a predetermined schedule as outlined in Table 2.

Table 2. Weeks 1 and 2 (14 Days) Pregabalin Dose Escalation Schedule

Final Dose	Days 1-3 (mg/day)	Days 4-7 (mg/day)	Days 8-11 (mg/day)	Day 12 onward (mg/day)
PGB 450 mg/day	75	150	300	450
PGB 300 mg/day	75	150	300	300
PGB 150 mg/day	75	150	150	150
PGB 100 mg/day	50	100	100	100
PGB 50 mg/day	No titration			
Placebo	Matching capsules			

PGB = pregabalin.

Thereafter, the dose level remained fixed for the duration of the double-blind treatment period. At the end of this period, starting at Day 1 of Week 7, pregabalin was tapered. A description of the taper schedule for each dose group is presented in Table 3.

Table 3. Week 7 Pregabalin Tapering Schedule

Final Dose	Days 1-3 (mg/day)	Days 4-6 (mg/day)	Day 7 (mg/day)
PGB 450 mg/day	300	150	75
PGB 300 mg/day	150	75	0
PGB 150 mg/day	75	0	0
PGB 100 mg/day	50	0	0
PGB 50 mg/day	0	0	0
Placebo mg/day	Matching capsules		

Table 3. Week 7 Pregabalin Tapering Schedule

Final Dose	Days 1-3 (mg/day)	Days 4-6 (mg/day)	Day 7 (mg/day)

PGB = pregabalin.

Throughout the study, dosing occurred 1-3 hours before the subject's typical bedtime for all treatment groups during double-blind treatment and the single-blind placebo run-in period.

Efficacy and Outcomes Research Endpoints:

Primary Efficacy: Change from baseline to endpoint in the RLS symptom severity using the IRLS total score at Week 6 with regard to dose level.

Secondary Efficacy and Outcome Measures:

- The proportion of subjects responding to treatment using the CGI-I scale at Week 6 with respect to dose level.
- Clinical Global Impression - Severity (CGI-S) scale.
- Subjective Sleep Questionnaire (SSQ).
- Medical Outcomes Study - Sleep scale (MOS-SS).
- RLS Quality of Life (RLS-QoL) scale.
- Medical Outcomes Study - Short Form 36 (SF-36).

Safety Evaluations: Safety evaluations included AE monitoring, laboratory evaluations, vital signs, electrocardiograms (ECGs), RLS symptom rebound, medical history, and physical examinations.

Statistical Methods:

Intent-to-Treat (ITT) population: Efficacy analyses were conducted for the ITT population, which was defined as the set of randomized subjects who took at least 1 dose of study medication and had at least 1 post-randomization efficacy assessment on any efficacy scale.

Safety Analysis Set: The safety population consists of subjects who took at least 1 dose of study medication.

Primary Efficacy Analysis: A dose-response modeling strategy was used to find a well-fitting, parsimonious model for the change in total IRLS score across the 6 dose levels at Week 6.

Secondary Efficacy Analyses:

The change from Baseline in the IRLS total score was analyzed with a linear mixed model using restricted maximum likelihood estimation. The least squares means and appropriate

standard errors used in performing 2-sided tests and constructing confidence intervals (CIs) for comparing pregabalin doses to placebo. Subjects who discontinued early were assumed to be missing at random when the prespecified primary analysis was employed. A pattern mixture model was employed as a sensitivity analysis to investigate the missing at random assumption. A last observation carried forward (LOCF) analysis was also used as a prespecified sensitivity analysis for the Week 6 assessments using 2-sided tests and CIs. The LOCF analysis included fixed terms for treatment and geographical region, and Baseline as a continuous covariate.

CGI-I Responders were defined as subjects having a CGI-I score of "very much improved" or "much improved." Responder status was analyzed using a Cochran-Mantel-Haenszel test stratified by geographical region. For subjects who discontinued early, prior to completion of the study, their last observed response was carried forward for Week 6. A sensitivity analysis was conducted using a multiple imputation approach to address the missing data at Week 6 for the CGI-I response.

Changes from Baseline for the continuous secondary endpoints were analyzed using a linear mixed model. The least squares means and appropriate standard errors were used in performing two-sided tests and constructing CIs for comparing pregabalin doses to placebo. The degrees of freedom for the tests and CIs were adjusted using a Kenward-Rogers correction.

A LOCF analysis for the last planned visit was also performed as a sensitivity analysis to assess the robustness of the linear mixed model analysis. The Baseline covariate adjustment used in both the linear mixed model and the LOCF approach corresponded to the secondary endpoint being analyzed. Discrete variables such as MOS optimal sleep and the CGI-S were analyzed using logistic regression or the Cochran-Mantel-Haenszel test stratified by geographical region.

RESULTS

Subject Disposition and Demography: A total of 137 subjects were assigned to study treatment and all 137 subjects received study treatment (23 in placebo; 22 in pregabalin 50 mg; 23 in pregabalin 100 mg; 22 in pregabalin 150 mg; 24 in pregabalin 300 mg; and 23 in pregabalin 450 mg). A summary of subject evaluation groups is provided in Table 4.

Table 4. Subject Evaluation Groups

Number of Subjects	Placebo	Pregabalin 50 mg	Pregabalin 100 mg	Pregabalin 150 mg	Pregabalin 300 mg	Pregabalin 450 mg
Screened: 218						
Assigned to study treatment	23	22	23	22	24	23
Treated	23	22	23	22	24	23
Completed	21	20	22	17	23	18
Discontinued	2	2	1	5	1	5
Related to study drug						
Adverse event	1	1	0	5	1	2
Not related to study drug	1	1	1	0	0	3
Adverse event	0	1	0	0	0	0
Lost to follow-up	0	0	0	0	0	1
Other[a]	1	0	1	0	0	1
Subject no longer willing to participate in study	0	0	0	0	0	1

a. Insufficient efficacy (placebo); lack of efficacy (Pregabalin 100 mg); protocol violation (Pregabalin 450 mg).

Demography: None of the subjects had presenting conditions or medical history that the Investigators considered sufficient to affect the conduct of the study or to represent a potential risk to the subject during study participation. A summary of demographic and Baseline characteristics is included in Table 5.

Table 5. Demographic and Baseline Characteristics

Number of Subjects	Placebo (N=23)	Pregabalin 50 mg (N=22)	Pregabalin 100 mg (N=23)	Pregabalin 150 mg (N=22)	Pregabalin 300 mg (N=24)	Pregabalin 450 mg (N=23)
Gender						
Male	10	9	7	9	5	7
Female	13	13	16	13	19	16
Age (years)						
Mean	50.3	50.5	47.4	52.2	49.6	54.8
SD	10.5	11.9	10.9	7.6	10.4	7.9
Range	25-63	24-66	22-64	27-62	29-64	39-65
Race						
White	22	21	21	21	20	21
Black	1	1	1	0	2	1
Asian	0	0	1	0	0	0
Other	0	0	0	1	2	1
Weight (kg)						
Mean	85.1	84.6	77.0	77.6	83.3	78.8
SD	17.5	18.1	14.9	13.8	17.1	14.1
Range	56.8-120.0	62.0-136.9	54.5-105.9	52.9-102.0	60.0-122.5	56.1-104.6
Height (cm)						
Mean	172.3	168.3	166.0	170.4	166.2	167.0
SD	10.2	10.3	10.2	9.5	8.2	8.0
Range	154.0-193.0	152.0-185.4	142.2-188.0	155.0-191.0	154.0-185.5	152.0-183.0

N = number of subjects; SD = standard deviation.

Efficacy and Outcomes Research Results:

Primary efficacy: Based on the nonlinear model, the dose providing 50% of the maximal effect (ED50) and the dose providing 90% of the maximal effect (ED90) were estimated for pregabalin using a bootstrap method and are presented in Table 6. The results from the dose-response analysis estimated that a dose of 123.9 mg/day (ie, median of the bootstrap distribution) is effective in producing a 90% of the maximal effect in reducing the RLS symptoms based on the IRLS.

Table 6. ED50 and ED90 Point Estimates

	ED50 (mg)	ED90 (mg)
N[a]	1946	1946
Mean (SD)	46.1 (64.3)	153.2 (213.5)
95% Confidence Interval	0.1, 157.7	0.4, 523.9
Median	37.3	123.9
25th-75th Percentile	21.5-54.3	71.5-180.2
90th Percentile	83.8	278.4
95th Percentile	119.4	396.5

The statistics were obtained from 3 parameter model. Y = D + G*exp(B*dose) by bootstrapping 2000 data sets. Nonconvergence for the nonlinear model occurred in 54 bootstrap samples, which were not included in summarizing ED50 and ED90 distribution or confidence interval.
ED50 = the dose providing 50% of the maximal effect; ED90 = the dose providing 90% of the maximal effect; SD = standard deviation.
a. Number of bootstrap samples where convergence occurred.

IRLS Total Score: Mixed model analysis of the observed change from baseline summarized at week 6, (ITT population) is presented in Table 7. At Week 6, decreases in the mean IRLS total score (LS mean) change from Baseline were greater at doses of 150 mg/day and above than placebo and lower doses and these changes were statistically significant at the nominal level ($p \leq 0.05$), except for the 300 mg/day group.

Table 7. IRLS Total Score – Mixed Model Analysis of the Observed Change From Baseline at Week 6 (ITT Population)

IRLS Total Score	Placebo (N=23)	Pregabalin 50 mg (N=22)	Pregabalin 100 mg (N=23)	Pregabalin 150 mg (N=22)	Pregabalin 300 mg (N=24)	Pregabalin 450 mg (N=23)
Change From Baseline to Week 6						
n	21	20	22	18	23	20
LS mean (SE)	-7.73 (1.720)	-11.83 (1.771)	-11.76 (1.694)	-16.02 (1.865)	-12.89 (1.713)	-16.26 (1.771)
Contrast vs Placebo						
LS mean difference		-4.10	-4.03	-8.29	-5.16	-8.53
95% LS mean difference		-8.97, 0.77	-8.78, 0.73	-13.31, -3.28	-9.96, -0.36	-13.40, -3.67
p-value		0.0983	0.0966	0.0013*	0.0353*	0.0006*

* = p-value ≤0.05.
The repeated measures model used fixed effects of treatment, geographic region, week, and treatment-by-week interaction. Baseline score was included as a covariate. Additionally, the model included subject as a repeated measurement block within which the covariance structure was assumed to be compound symmetric.
IRLS = International Restless Legs Group Rating Scale; ITT = intent-to-treat; LS = least squares; N = number of subjects randomized and received at least 1 dose of study drug; n = number of subjects who were randomized and received at least 1 dose of study drug, and had Baseline and postbaseline values; SE = standard error, vs = versus.

Secondary Efficacy: A summary of CGI-I responders is provided in Table 8. The percentage of CGI-I Responders at the end of double-blind treatment (Week 6) was highest for the 300 and 450 mg/day dose groups with values of 73.9% and 90.0%, respectively.

Table 8. CGI-I Responders at Week 6 and Last Observation – ITT Population

CGI-I Responder Status	Placebo (N=23) n (%)	Pregabalin 50 mg (N=22) n (%)	Pregabalin 100 mg (N=23) n (%)	Pregabalin 150 mg (N=22) n (%)	Pregabalin 300 mg (N=24) n (%)	Pregabalin 450 mg (N=23) n (%)
Week 6						
Number assessed	21	20	22	18	23	20
Responders	13 (61.9)	12 (60.0)	15 (68.2)	11 (61.1)	17 (73.9)	18 (90.0)
Last observation						
Number assessed	23	22	23	22	24	23
Responders	13 (56.5)	12 (54.5)	15 (65.2)	11 (50.0)	17 (70.8)	20 (87.0)

CGI-I = Clinical Global Impressions-Improvement; ITT = intent-to-treat; N = number of subjects in a treatment group; n = number of subjects with CGI-I rating.

A summary of CGI-S score at Baseline and at Week 6 is provided in Table 9.

Table 9. CGI-S Score at Baseline and at Week 6 – ITT Population

Global Improvement	Placebo (N=23) n (%)	Pregabalin 50 mg (N=22) n (%)	Pregabalin 100 mg (N=23) n (%)	Pregabalin 150 mg (N=22) n (%)	Pregabalin 300 mg (N=24) n (%)	Pregabalin 450 mg (N=23) n (%)
Baseline						
n	23	22	23	22	24	23
Normal, not at all ill	0	0	0	0	0	0
Borderline ill	0	0	0	0	0	0
Mildly ill	1 (4.3)	1 (4.5)	2 (8.7)	4 (18.2)	2 (8.3)	2 (8.7)
Moderately ill	6 (26.1)	9 (40.9)	8 (34.8)	5 (22.7)	11 (45.8)	6 (26.1)
Markedly ill	7 (30.4)	8 (36.4)	7 (30.4)	5 (22.7)	3 (12.5)	5 (21.7)
Severely ill	8 (34.8)	3 (13.6)	6 (26.1)	7 (31.8)	8 (33.3)	10 (43.5)
Among the most extremely ill	1 (4.3)	1 (4.5)	0	1 (4.5)	0	0
Week 6						
n	21	20	22	18	23	20
Normal, not at all ill	1 (4.8)	3 (15.0)	4 (18.2)	4 (22.2)	6 (26.1)	7 (35.0)
Borderline ill	3 (14.3)	3 (15.0)	4 (18.2)	4 (22.2)	4 (17.4)	5 (25.0)
Mildly ill	11 (52.4)	6 (30.0)	7 (31.8)	7 (38.9)	7 (30.4)	6 (30.0)
Moderately ill	2 (9.5)	5 (25.0)	5 (22.7)	3 (16.7)	1 (4.3)	1 (5.0)
Markedly ill	2 (9.5)	2 (10.0)	2 (9.1)	0	4 (17.4)	1 (5.0)
Severely ill	2 (9.5)	1 (5.0)	0	0	1 (4.3)	0
Among the most extremely ill	0	0	0	0	0	0

ITT = intent-to-treat; N = number of subjects; n=number of subjects with clinical global impressions-severity (CGI-S) rating.

Summaries of SSQ scores for Quality of Sleep and Latency are provided in Table 10 and Table 11 respectively. The SSQ item of Sleep Quality showed numeric improvements across doses and time. However, a consistent pattern of nominal p-values ≤0.05 was not observed.

Table 10. SSQ - Quality of Sleep: Mixed Model Analysis of the Observed Change From Baseline Summarized by Week, ITT Population

Treatment	N	n	Min	Median	Max	Mean (SD)	LS Mean (SE)	Contrast of Treatment Versus Placebo Difference (SE)	95% CI	p-value
Baseline										
Placebo	23	23	8	40.7	71	39.2 (16.91)				
Pregabalin 50 mg/day	22	22	5	38.9	74	35.3 (19.61)				
Pregabalin 100 mg/day	23	23	7	40.3	71	40.0 (19.24)				
Pregabalin 150 mg/day	22	22	2	36.8	56	33.2 (16.44)				
Pregabalin 300 mg/day	24	24	2	29.4	70	32.3 (18.75)				
Pregabalin 450 mg/day	23	23	1	41.0	75	41.0 (19.52)				
Week 1										
Placebo	23	23	-16	5.9	31	4.1 (9.84)	5.0 (4.10)			
Pregabalin 50 mg/day	22	22	-24	15.1	80	19.0 (22.88)	18.8 (4.21)	13.8 (5.89)	(2.2, 25.4)	0.0199
Pregabalin 100 mg/day	23	23	-13	8.6	53	14.1 (14.65)	15.2 (4.10)	10.3 (5.78)	(-1.1, 21.7)	0.0768
Pregabalin 150 mg/day	22	22	-21	16.0	50	16.9 (17.52)	15.9 (4.23)	11.0 (5.91)	(-0.7, 22.6)	0.0642
Pregabalin 300 mg/day	24	24	-7	14.5	37	12.6 (10.29)	11.5 (4.16)	6.6 (5.88)	(-5.0, 18.2)	0.2643
Pregabalin 450 mg/day	23	23	-12	16.0	46	15.5 (15.61)	17.2 (4.11)	12.2 (5.80)	(0.8, 23.7)	0.0358
Week 2										
Placebo	23	23	-12	11.5	46	10.4 (13.54)	11.3 (4.10)			
Pregabalin 50 mg/day	22	21	-3	12.1	82	23.4 (26.64)	23.3 (4.27)	12.1 (5.93)	(0.4, 23.8)	0.0428
Pregabalin 100 mg/day	23	22	-7	15.6	44	18.2 (13.96)	18.7 (4.13)	7.5 (5.81)	(-4.0, 18.9)	0.1993
Pregabalin 150 mg/day	22	19	-10	24.3	87	26.1 (25.53)	24.2 (4.4)	12.9 (6.04)	(1.1, 24.8)	0.0331
Pregabalin 300 mg/day	24	23	-4	21.4	58	24.5 (14.95)	23.4 (4.20)	12.1 (5.91)	(0.5, 23.8)	0.0415
Pregabalin 450 mg/day	23	22	-16	15.9	67	22.3 (21.89)	24.0 (4.16)	12.8 (5.83)	(1.3, 24.3)	0.0295
Week 3										
Placebo	23	21	-6	11.4	52	12.7 (14.51)	13.8 (4.17)			
Pregabalin 50 mg/day	22	20	-32	16.5	83	23.8 (30.31)	23.0 (4.31)	9.2 (6.01)	(-2.6, 21.1)	0.1267
Pregabalin 100 mg/day	23	23	-8	17.7	42	17.4 (14.13)	18.6 (4.10)	4.7 (5.84)	(-6.8, 16.2)	0.4175
Pregabalin 150 mg/day	22	19	-20	22.1	93	28.7 (27.50)	26.8 (4.40)	13.0 (6.09)	(1.0, 25.0)	0.0342
Pregabalin 300 mg/day	24	23	8	24.4	57	24.7 (11.84)	23.6 (4.20)	9.7 (5.96)	(-2.0, 21.5)	0.1038
Pregabalin 450 mg/day	23	19	-13	24.1	67	26.4 (21.61)	25.4 (4.29)	11.6 (5.98)	(-0.2, 23.4)	0.0537
Week 4										
Placebo	23	22	-15	10.3	63	12.2 (19.36)	13.2 (4.14)			
Pregabalin 50 mg/day	22	20	-15	17.6	83	24.5 (28.50)	23.8 (4.31)	10.6 (5.99)	(-1.2, 22.4)	0.0772
Pregabalin 100 mg/day	23	23	-9	20.3	54	20.9 (17.90)	22.0 (4.10)	8.8 (5.81)	(-2.6, 20.3)	0.1296

Table 10. SSQ - Quality of Sleep: Mixed Model Analysis of the Observed Change From Baseline Summarized by Week, ITT Population

Treatment	N	n	Min	Median	Max	Mean (SD)	LS Mean (SE)	Contrast of Treatment Versus Placebo Difference (SE)	95% CI	p-value
Pregabalin 150 mg/day	22	19	-30	20.9	95	30.0 (28.46)	28.2 (4.40)	15.0 (6.06)	(3.1, 27.0)	0.0140
Pregabalin 300 mg/day	24	23	-2	25.0	73	25.4 (17.36)	24.2 (4.20)	11.0 (5.93)	(-0.7, 22.7)	0.0642
Pregabalin 450 mg/day	23	20	-29	23.4	64	23.1 (24.56)	23.8 (4.25)	10.7 (5.92)	(-1.0, 22.3)	0.0730
Week 5										
Placebo	23	21	-23	11.1	59	13.9 (20.58)	14.7 (4.17)			
Pregabalin 50 mg/day	22	20	-15	24.4	85	29.4 (28.64)	28.7 (4.31)	13.9 (6.01)	(2.1, 25.8)	0.0215
Pregabalin 100 mg/day	23	23	-7	14.3	51	18.7 (16.31)	19.9 (4.10)	5.2 (5.84)	(-6.4, 16.7)	0.3785
Pregabalin 150 mg/day	22	18	-14	31.6	96	33.4 (25.90)	30.9 (4.45)	16.1 (6.12)	(4.1, 28.2)	0.0089
Pregabalin 300 mg/day	24	23	-4	24.7	66	27.1 (17.74)	26.0 (4.20)	11.2 (5.96)	(-0.5, 23.0)	0.0609
Pregabalin 450 mg/day	23	20	-27	27.9	92	30.3 (28.35)	31.1 (4.25)	16.4 (5.95)	(4.7, 28.1)	0.0064
Week 6										
Placebo	23	21	-25	8.7	59	13.1 (20.28)	13.9 (4.17)			
Pregabalin 50 mg/day	22	20	-11	26.3	76	28.3 (24.99)	27.6 (4.31)	13.7 (6.01)	(1.8, 25.5)	0.0241
Pregabalin 100 mg/day	23	22	-5	17.9	53	23.3 (15.91)	23.5 (4.14)	9.6 (5.86)	(-2.0, 21.1)	0.1032
Pregabalin 150 mg/day	22	17	12	25.7	93	35.2 (24.41)	30.5 (4.50)	16.6 (6.16)	(4.4, 28.7)	0.0076
Pregabalin 300 mg/day	24	23	-8	17.1	77	24.2 (19.90)	23.1 (4.20)	9.2 (5.96)	(-2.6, 20.9)	0.1257
Pregabalin 450 mg/day	23	20	-33	24.5	87	28.0 (27.88)	28.8 (4.25)	14.9 (5.95)	(3.2, 26.6)	0.0131

The repeated measures model used fixed effects of treatment, geographic region, week and treatment by week interaction. Baseline score was included as a covariate. Additionally, the model included subject as a repeated measurement block within which the covariance structure was assumed to be compound symmetric (CS). Baseline statistics have been calculated only for subjects who have non-missing change from baseline at at least 1 postbaseline visit.
CI = confidence interval; LS Mean = least squares mean, Max =maximum, Min = minimum; N = number of subjects; n = number of subjects with subjective sleep questionnaire (SSQ); SE = standard error; SD = standard deviation, Difference (SE): Pregabalin - Placebo.

Table 11. SSQ - Latency: Mixed Model Analysis of the Observed Change From Baseline Summarized by Week, ITT Population

Treatment	N	n	Min	Median	Max	Mean (SD)	LS Mean (SE)	Contrast of Treatment Versus Placebo Difference (SE)	95% CI	p-value
Baseline										
Placebo	23	23	12	53.6	134	57.5 (36.20)				
Pregabalin 50 mg/day	22	22	13	41.1	209	61.0 (52.08)				
Pregabalin 100 mg/day	23	23	4	45	169	61.7 (51.15)				
Pregabalin 150 mg/day	22	22	6	46.8	129	49.4 (37.14)				
Pregabalin 300 mg/day	24	24	10	42.8	217	64.2 (54.70)				
Pregabalin 450 mg/day	23	23	5	35.8	198	59.9 (59.77)				
Week 1										
Placebo	23	23	-76	-7.1	41	-9.3 (22.65)	-9.8 (5.60)			
Pregabalin 50 mg/day	22	22	-119	-5.4	48	-18.1 (35.88)	-16.3 (5.76)	-6.6 (8.05)	(-22.4, 9.3)	0.4133
Pregabalin 100 mg/day	23	23	-60	-14.1	32	-14.7 (24.90)	-13.2 (5.60)	-3.4 (7.92)	(-19.0, 12.2)	0.6676
Pregabalin 150 mg/day	22	22	-76	-6.1	49	-6.8 (26.29)	-10.4 (5.76)	-0.7 (8.04)	(-16.5, 15.2)	0.9355
Pregabalin 300 mg/day	24	24	-109	-13.7	54	-12.8 (32.54)	-9.1 (5.65)	0.6 (7.97)	(-15.1, 16.4)	0.9355
Pregabalin 450 mg/day	23	23	-158	-8.9	12	-21.3 (37.78)	-20.2 (5.62)	-10.5 (7.94)	(-26.1, 5.2)	0.1895
Week 2										
Placebo	23	23	-47	-5.7	38	-8.4 (18.70)	-8.9 (5.60)			
Pregabalin 50 mg/day	22	21	-167	-8.7	50	-21.3 (48.93)	-20.7 (5.84)	-11.9 (8.10)	(-27.8, 4.1)	0.1443
Pregabalin 100 mg/day	23	22	-69	-15	18	-19.9 (23.58)	-17.2 (5.65)	-8.4 (7.96)	(-24.0, 7.3)	0.2946
Pregabalin 150 mg/day	22	19	-96	-12.9	73	-12.8 (35.90)	-16.3 (6.00)	-7.4 (8.22)	(-23.6, 8.8)	0.3686
Pregabalin 300 mg/day	24	23	-67	-14.7	55	-13.1 (32.64)	-13.0 (5.71)	-4.1 (8.02)	(-19.9, 11.7)	0.6079
Pregabalin 450 mg/day	23	22	-178	-16.2	10	-36.0 (47.81)	-34.3 (5.69)	-25.5 (7.99)	(-41.2, -9.7)	0.0016
Week 3										
Placebo	23	21	-91	-10.7	29	-14.4 (25.25)	-14.6 (5.71)			
Pregabalin 50 mg/day	22	20	-124	-4.2	19	-20.2 (35.97)	-18.9 (5.90)	-4.3 (8.22)	(-20.5, 11.8)	0.5976
Pregabalin 100 mg/day	23	23	-59	-10	11	-14.6 (18.79)	-13.1 (5.60)	1.5 (8.00)	(-14.3, 17.3)	0.8527
Pregabalin 150 mg/day	22	19	-94	-8.6	54	-14.4 (35.29)	-17.8 (6.00)	-3.2 (8.29)	(-19.6, 13.1)	0.6973
Pregabalin 300 mg/day	24	23	-67	-15.7	35	-18.0 (25.79)	-17.8 (5.71)	-3.2 (8.09)	(-19.2, 12.7)	0.6895
Pregabalin 450 mg/day	23	19	-161	-16.4	12	-37.8 (50.39)	-33.7 (5.88)	-19.1 (8.21)	(-35.2, -2.9)	0.0209
Week 4										
Placebo	23	22	-85	-5.4	11	-12.9 (23.64)	-13.6 (5.66)			
Pregabalin 50 mg/day	22	20	-124	-2.4	19	-21.6 (37.64)	-20.4 (5.90)	-6.8 (8.18)	(-22.9, 9.3)	0.4084
Pregabalin 100 mg/day	23	23	-101	-15.7	24	-21.9 (26.99)	-20.4 (5.60)	-6.8 (7.96)	(-22.5, 8.9)	0.3958

Table 11. SSQ - Latency: Mixed Model Analysis of the Observed Change From Baseline Summarized by Week, ITT Population

Treatment	N	n	Min	Median	Max	Mean (SD)	LS Mean (SE)	Contrast of Treatment Versus Placebo Difference (SE)	95% CI	p-value
Pregabalin 150 mg/day	22	19	-96	-10	71	-14.8 (38.61)	-18.2 (6.00)	-4.6 (8.25)	(-20.9, 11.7)	0.5776
Pregabalin 300 mg/day	24	23	-100	-16.4	56	-18.3 (32.17)	-18.2 (5.71)	-4.6 (8.06)	(-20.5, 11.3)	0.5665
Pregabalin 450 mg/day	23	20	-172	-16.1	36	-39.5 (55.86)	-37.1 (5.82)	-23.5 (8.13)	(-39.6, -7.5)	0.0041
Week 5										
Placebo	23	21	-80	-5.8	6	-15.5 (23.23)	-15.9 (5.71)			
Pregabalin 50 mg/day	22	20	-137	-7.3	9	-28.0 (41.44)	-26.8 (5.90)	-10.9 (8.22)	(-27.1, 5.2)	0.1842
Pregabalin 100 mg/day	23	23	-61	-11.4	4	-19.2 (19.22)	-17.6 (5.60)	-1.8 (8.00)	(-17.5, 14.0)	0.8269
Pregabalin 150 mg/day	22	18	-82	-13.6	71	-20.1 (33.66)	-24.0 (6.07)	-8.1 (8.34)	(-24.5, 8.3)	0.3319
Pregabalin 300 mg/day	24	23	-125	-15.7	72	-13.5 (42.82)	-13.4 (5.71)	2.5 (8.09)	(-13.4, 18.5)	0.7552
Pregabalin 450 mg/day	23	20	-179	-18.4	14	-38.5 (49.35)	-36.1 (5.82)	-20.3 (8.16)	(-36.3, -4.2)	0.0137
Week 6										
Placebo	23	21	-61	-7.6	31	-12.0 (19.27)	-12.4 (5.71)			
Pregabalin 50 mg/day	22	20	-129	-9	18	-26.6 (39.90)	-25.4 (5.90)	-13.0 (8.22)	(-29.2, 3.2)	0.1157
Pregabalin 100 mg/day	23	22	-61	-13.9	4	-21.2 (20.19)	-19.5 (5.65)	-7.1 (8.04)	(-22.9, 8.7)	0.3791
Pregabalin 150 mg/day	22	17	-105	-8.9	19	-24.4 (34.11)	-25.1 (6.14)	-12.7 (8.39)	(-29.2, 3.9)	0.1329
Pregabalin 300 mg/day	24	23	-100	-16.4	91	-10.2 (44.10)	-10.1 (5.71)	2.3 (8.09)	(-13.6, 18.3)	0.7723
Pregabalin 450 mg/day	23	20	-184	-18.4	8	-37.3 (48.14)	-34.9 (5.82)	-22.5 (8.16)	(-38.6, -6.4)	0.0063

The repeated measures model used fixed effects of treatment, geographic region, week and treatment by week interaction. Baseline score was included as a covariate. Additionally, the model included subject as a repeated measurement block within which the covariance structure was assumed to be compound symmetric (CS). Baseline statistics have been calculated only for subjects who have non-missing change from baseline at at least 1 postbaseline visit.
CI = confidence interval; LS Mean = least squares mean, Max =maximum, Min = minimum; N = number of subjects; n = number of subjects with subjective sleep questionnaire (SSQ); SE = standard error; SD = standard deviation, Difference (SE): Pregabalin - Placebo.

Dose response relationships on the MOS-SS were not clearly evident. For the subscales of Sleep Disturbance, Sleep Adequacy and the 6- and 9-item Sleep Problems Indices, both the frequency of significant changes observed for the 450 mg dose, as early as Week 2, and the numerical trends observed for other doses over the course of the study suggested that higher doses of pregabalin may have a greater effect on some MOS-SS domains. A Summary of MOS-SS sleep disturbance scores is provided in Table 12.

Table 12. MOS-SS - Sleep Disturbance: Mixed Model Analysis of the Observed Change From Baseline Summarized by Week, ITT Population

Treatment	N	n	Min	Median	Max	Mean (SD)	LS Mean (SE)	Contrast of Treatment Versus Placebo		
								Difference (SE)	95% CI	p-value
Baseline										
Placebo	23	23	20	69.0	100	65.3 (25.02)				
Pregabalin 50 mg/day	22	21	26	58.0	100	60.6 (21.36)				
Pregabalin 100 mg/day	23	23	10	75.0	100	64.7 (29.86)				
Pregabalin 150 mg/day	22	20	10	52.5	100	57.1 (27.87)				
Pregabalin 300 mg/day	24	24	21	69.0	100	69.8 (24.75)				
Pregabalin 450 mg/day	23	22	20	59.5	100	57.3 (23.86)				
Week 1										
Placebo	23	23	-54	-10.0	28	-10.3 (17.66)	-9.0 (4.76)			
Pregabalin 50 mg/day	22	20	-78	-19.0	27	-18.8 (23.56)	-18.2 (5.05)	-9.3 (6.94)	(-23.0, 4.4)	0.1824
Pregabalin 100 mg/day	23	21	-90	-26.0	28	-24.2 (29.90)	-21.1 (4.87)	-12.1 (6.80)	(-25.5, 1.3)	0.0767
Pregabalin 150 mg/day	22	18	-55	-20.0	15	-19.6 (20.67)	-23.0 (5.26)	-14.1 (7.11)	(-28.1, -0.1)	0.0492
Pregabalin 300 mg/day	24	23	-69	-20.0	11	-22.4 (23.76)	-17.7 (4.93)	-8.7 (6.84)	(-22.2, 4.7)	0.2023
Pregabalin 450 mg/day	23	22	-63	-21.5	25	-24.4 (21.76)	-26.3 (4.89)	-17.4 (6.83)	(-30.9, -3.9)	0.0116
Week 2										
Placebo	23	23	-64	-17.0	11	-17.1 (20.24)	-15.7 (4.76)			
Pregabalin 50 mg/day	22	19	-78	-23.0	22	-23.2 (25.38)	-25.1 (5.14)	-9.4 (7.01)	(-23.2, 4.4)	0.1819
Pregabalin 100 mg/day	23	22	-95	-18.0	10	-25.5 (28.73)	-23.0 (4.81)	-7.3 (6.76)	(-20.6, 6.0)	0.2806
Pregabalin 150 mg/day	22	18	-100	-25.0	24	-25.0 (34.12)	-26.1 (5.30)	-10.4 (7.13)	(-24.4, 3.7)	0.1465
Pregabalin 300 mg/day	24	23	-88	-37.0	5	-41.2 (24.65)	-35.3 (4.95)	-19.6 (6.85)	(-33.1, -6.1)	0.0046
Pregabalin 450 mg/day	23	20	-68	-25.0	15	-30.0 (25.35)	-32.1 (5.02)	-16.4 (6.92)	(-30.0, -2.8)	0.0187
Week 4										
Placebo	23	22	-63	-21.5	0	-23.7 (19.32)	-22.0 (4.81)			
Pregabalin 50 mg/day	22	20	-78	-12.5	26	-17.6 (29.91)	-18.5 (5.07)	3.5 (7.00)	(-10.2, 17.3)	0.6128
Pregabalin 100 mg/day	23	23	-89	-20.0	11	-29.4 (29.92)	-28.3 (4.76)	-6.4 (6.76)	(-19.7, 7.0)	0.3488
Pregabalin 150 mg/day	22	18	-100	-33.5	20	-31.3 (32.04)	-32.4 (5.30)	-10.4 (7.17)	(-24.5, 3.7)	0.1472
Pregabalin 300 mg/day	24	23	-94	-46.0	19	-40.0 (28.20)	-34.2 (4.95)	-12.2 (6.89)	(-25.7, 1.4)	0.0791
Pregabalin 450 mg/day	23	20	-73	-26.5	8	-33.2 (21.85)	-37.4 (5.02)	-15.4 (6.97)	(-29.1, -1.7)	0.0282
Week 6										
Placebo	23	21	-62	-20.0	20	-21.7 (18.69)	-19.3 (4.87)			
Pregabalin 50 mg/day	22	19	-78	-27.0	5	-29.3 (25.91)	-29.2 (5.14)	-9.9 (7.08)	(-23.9, 4.0)	0.1623
Pregabalin 100 mg/day	23	22	-88	-20.0	23	-26.8 (30.71)	-25.3 (4.81)	-6.1 (6.84)	(-19.6, 7.4)	0.3739

Table 12. MOS-SS - Sleep Disturbance: Mixed Model Analysis of the Observed Change From Baseline Summarized by Week, ITT Population

Treatment	N	n	Min	Median	Max	Mean (SD)	LS Mean (SE)	Contrast of Treatment Versus Placebo		
								Difference (SE)	95% CI	p-value
Pregabalin 150 mg/day	22	17	-90	-31.0	7	-31.9 (30.71)	-33.4 (5.38)	-14.2 (7.26)	(-28.5, 0.1)	0.0517
Pregabalin 300 mg/day	24	23	-94	-35.0	20	-37.3 (29.80)	-31.4 (4.95)	-12.1 (6.92)	(-25.8, 1.5)	0.0815
Pregabalin 450 mg/day	23	20	-68	-29.0	-5	-36.0 (22.20)	-40.2 (5.02)	-20.9 (7.00)	(-34.7, -7.1)	0.0031

The repeated measures model used fixed effects of treatment, geographic region, week and treatment by week interaction. Baseline score was included as a covariate. Additionally, the model included subject as a repeated measurement block within which the covariance structure was assumed to be compound symmetric (CS). Baseline statistics have been calculated only for subjects who have non-missing change from baseline at at least 1 postbaseline visit.
CI = confidence interval; LS Mean = least squares mean, Max =maximum, Min = minimum; MOSS-SS = medical outcomes study - sleep scale; N = number of subjects; n = number of subjects with MOS-SS; SE = standard error; SD = standard deviation, Difference (SE): Pregabalin - Placebo.

A summary of RLS-QoL Summary Score is provided in Table 13. There were numerical differences in favor of pregabalin tending toward improvements in quality of life, as measured by the RLS-QoL, at Week 6. The RLS–QoL summary score showed improvement across doses. However, these changes did not reach a nominal p-value ≤0.05.

Table 13. RLS-QoL Summary Score: Analysis of Covariance of the Change From Baseline at Week 6 (Observed Cases) and at the Last Observation (LOCF), ITT Population

	Placebo (N=23)	Pregabalin 50 mg (N=22)	Pregabalin 100 mg (N=23)	Pregabalin 150 mg (N=22)	Pregabalin 300 mg (N=24)	Pregabalin 450 mg (N=23)
Baseline						
n	21	20	23	21	24	21
Mean	61.0	55.3	54.0	63.7	62.1	65.5
SD	19.88	13.33	19.87	19.15	23.22	23.95
Median	62.5	58.8	57.5	65.0	68.8	70.0
Minimum	10	28	18	23	13	13
Maximum	98	78	95	90	95	93
Week 6						
n	20	19	22	18	23	20
Mean	76.9	77.2	80.5	81.5	76.1	83.0
SD	17.17	14.62	18.46	16.39	25.60	17.16
Median	81.3	77.5	85.0	80.0	85.0	88.8
Minimum	48	48	40	45	13	33
Maximum	98	100	100	100	100	100
Change From Baseline to Week 6						
n	20	19	22	18	23	20
Mean	13.4	22.0	24.9	19.7	14.5	17.5
SD	13.77	16.64	21.80	19.66	23.13	20.57
Median	13.8	17.5	21.3	15.0	15.0	16.3
Minimum	-8	-5	-13	-15	-35	-15
Maximum	48	53	78	65	85	78
LS Mean	15.0	19.6	22.4	20.8	15.9	20.5
SE	3.71	3.87	3.55	3.94	3.63	3.74
LS Mean Difference		4.6	7.3	5.8	0.9	5.4
95% LS Mean Difference		(-6.0, 15.2)	(-2.9, 17.5)	(-4.9, 16.5)	(-9.4, 11.1)	(-5.0, 15.8)
P-value		0.3932	0.1585	0.285	0.8645	0.3031
Last Observation						
n	21	20	23	21	24	21
Mean	73.7	76.3	77.4	81.4	75.5	82.5
SD	22.20	14.90	23.26	15.40	25.19	16.88
Median	80.0	77.5	85.0	85.0	85.0	87.5
Minimum	10	48	10	45	13	33
Maximum	98	100	100	100	100	100
Change From Baseline to Last Observation						
n	21	20	23	21	24	21
Mean	12.7	21.0	23.4	17.7	13.4	17.0
SD	13.74	16.77	22.51	19.41	23.17	20.17
Median	12.5	16.3	20.0	15.0	15.0	15.0
Minimum	-8	-5	-13	-15	-35	-15
Maximum	48	53	78	65	85	78
LS Mean	13.1	18.8	20.5	19.5	14.5	19.6
SE	3.79	3.97	3.66	3.83	3.68	3.82
LS Mean Difference		5.7	7.4	6.4	1.5	6.5
95% LS Mean Difference		(-5.1, 16.6)	(-3.1, 17.8)	(-4.3, 17.0)	(-9.0, 11.9)	(-4.2, 17.1)
P-value		0.2990	0.1644	0.2370	0.7834	0.2311

Table 13. RLS-QoL Summary Score: Analysis of Covariance of the Change From Baseline at Week 6 (Observed Cases) and at the Last Observation (LOCF), ITT Population

The LS Mean, SE, 95% CI and P-value were from an analysis of covariance (ANCOVA) with treatment and geographic region as main effects and baseline value as covariate in the model.
LS Mean Difference: Pregabalin - Placebo.
CI = confidence interval; LS Mean = least squares mean; N = subjects who were randomized and received at least one dose of study drug; n (Baseline) = subjects who were randomized and received at least 1 dose of study drug, had baseline and postbaseline values, RLS = restless legs syndrome; SD = standard error; SE = standard error.

Dose response relationships on the SF-36 were not clearly evident. On those subscales where changes were seen that approached nominal p-values ≤0.05, it was generally at the 450 mg dose suggesting that higher doses of pregabalin may have a greater effect on some SF-36 domains. Summaries of MOS- SF-36 scores are provided in Table 14 for physical functioning and role-physical analysis, Table 15 for bodily pain and general health: analysis, Table 16 for vitality and social functioning analysis, Table 17 for role emotional and mental health analysis, Table 18 for summary physical score and summary emotional score analysis and Table 19 for self-evaluated summary.

Table 14. SF-36 - Physical Functioning and Role-Physical: Analysis of Covariance of the Change From Baseline at Week 6 (Observed Cases) and at the Last Observation (LOCF), ITT Population

	Physical Functioning						Role-Physical					
	Placebo (N=23) n (%)	Preg 50 mg (N=22) n (%)	Preg 100 mg (N=23) n (%)	Preg 150 mg (N=22) n (%)	Preg 300 mg (N=24) n (%)	Preg 450 mg (N=23) n (%)	Placebo (N=23) n (%)	Preg 50 mg (N=22) n (%)	Preg 100 mg (N=23) n (%)	Preg 150 mg (N=22) n (%)	Preg 300 mg (N=24) n (%)	Preg 450 mg (N=23) n (%)
Baseline												
n	22	20	23	20	24	21	22	20	23	20	24	21
Mean	80.7	80.5	80.4	88.0	78.8	79.8	72.7	76.9	72.8	73.1	78.6	71.7
SD	21.29	20.45	17.70	20.86	24.51	23.85	25.26	19.57	25.18	24.59	24.38	27.99
Median	82.5	90.0	85.0	97.5	85.0	90.0	75.0	81.3	81.3	78.1	87.5	75.0
Minimum	20	35	40	30	10	25	25	31	25	13	13	25
Maximum	100	100	100	100	100	100	100	100	100	100	100	100
Week 6												
n	21	19	22	17	23	20	21	19	22	17	23	20
Mean	84.8	80.5	83.2	85	82	84	76.2	82.9	82.4	80.5	78.3	83.8
SD	21.71	23.09	18.93	24.49	26.36	18.04	25.28	19.53	19.92	24.29	29.55	25.44
Median	95.0	85.0	90.0	95.0	90.0	87.5	87.5	87.5	87.5	93.8	93.8	100.0
Minimum	30	20	35	15	10	30	13	31	38	31	0	25
Maximum	100	100	100	100	100	100	100	100	100	100	100	100
Change From Baseline to Week 6												
n	21	19	22	17	23	20	21	19	22	17	23	20
Mean	3.6	0.8	2.5	-2.4	3.5	3.8	1.2	6.6	7.7	9.2	-0.5	10.3
SD	12.86	10.84	10.77	27.45	14.18	22.93	17.64	19.48	17.46	33.30	17.77	22.05
Median	0.0	0.0	2.5	0.0	0.0	0.0	0.0	0.0	6.3	6.3	0.0	3.1
Minimum	-25	-25	-25	-85	-30	-55	-44	-19	-38	-50	-38	-31
Maximum	35	15	25	60	40	55	31	69	44	81	50	56
LS Mean	3.6	0.5	2.4	-0.4	2.9	3.6	1.1	7.0	7.5	7.7	0.9	9.6
SE	3.50	3.71	3.42	3.93	3.52	3.62	4.24	4.49	4.14	4.77	4.24	4.40
LS Mean Difference		-3.1	-1.2	-4.1	-0.7	-0.0		5.9	6.4	6.6	-0.3	8.5
95% LS Mean Difference		(-13.2, 7.0)	(-10.9, 8.5)	(-14.5, 6.4)	(-10.5, 9.1)	(-10.0, 9.9)		(-6.3, 18.1)	(-5.4, 18.1)	(-6.1, 19.2)	(-12.1, 11.5)	(-3.6, 20.6)
P-value		0.5384	0.8015	0.4429	0.8860	0.9963		0.3421	0.2849	0.3058	0.9604	0.1661
Last Observation												
n	22	20	23	20	24	21	22	20	23	20	24	21
Mean	85.0	81.0	83.5	86.0	82.3	83.6	73.0	83.1	80.7	80.9	78.1	82.1
SD	21.21	22.57	18.55	23.09	25.83	17.69	28.83	19.03	21.06	22.89	28.91	25.87
Median	95.0	87.5	90.0	97.5	90.0	85.0	84.4	87.5	87.5	90.6	90.6	100

Table 14. SF-36 - Physical Functioning and Role-Physical: Analysis of Covariance of the Change From Baseline at Week 6 (Observed Cases) and at the Last Observation (LOCF), ITT Population

	Physical Functioning						Role-Physical					
	Placebo (N=23) n (%)	Preg 50 mg (N=22) n (%)	Preg 100 mg (N=23) n (%)	Preg 150 mg (N=22) n (%)	Preg 300 mg (N=24) n (%)	Preg 450 mg (N=23) n (%)	Placebo (N=23) n (%)	Preg 50 mg (N=22) n (%)	Preg 100 mg (N=23) n (%)	Preg 150 mg (N=22) n (%)	Preg 300 mg (N=24) n (%)	Preg 450 mg (N=23) n (%)
Minimum	30	20	35	15	10	30	6	31	38	31	0	25
Maximum	100	100	100	100	100	100	100	100	100	100	100	100
Change From Baseline to Last Observation												
n	22	20	23	20	24	21	22	20	23	20	24	21
Mean	4.3	0.5	3.0	-2.0	3.5	3.8	0.3	6.3	7.9	7.8	-0.5	10.4
SD	13.03	10.63	10.84	25.20	13.87	22.36	17.73	19.02	17.09	30.81	17.38	21.50
Median	0.0	0.0	5.0	0.0	0.0	0.0	0.0	0.0	6.3	6.3	0.0	6.3
Minimum	-25	-25	-25	-85	-30	-55	-44	-19	-38	-50	-38	-31
Maximum	35	15	25	60	40	55	31	69	44	81	50	56
LS Mean	4.2	0.5	2.8	0.1	3.1	3.5	-0.3	7.0	7.3	7.2	0.8	9.4
SE	3.33	3.52	3.25	3.53	3.31	3.43	4.09	4.32	4.00	4.33	4.05	4.22
LS Mean Difference		-3.7	-1.4	-4.0	-1.0	-0.6		7.3	7.6	7.5	1.1	9.7
95% LS Mean Difference		(-13.3, 5.9)	(-10.6, 7.8)	(-13.6, 5.6)	(-10.3, 8.3)	(-10.1, 8.8)		(-4.4, 19.1)	(-3.7, 19.0)	(-4.2, 19.3)	(-10.3, 12.5)	(-1.9, 21.3)
P-value		0.4456	0.7689	0.4083	0.8292	0.8929		0.2206	0.1834	0.2069	0.8529	0.1016

The LS Mean, SE, 95% CI and P-value were from an analysis of covariance (ANCOVA) with treatment and geographic region as main effects and baseline value as covariate in the model.
LS Mean Difference: Pregabalin – Placebo; SF-36: Medical Outcome Study - Short Form 36.
CI = confidence interval; ITT = intent to treat; LS Mean = least squares mean; N = subjects who were randomized and received at least 1 dose of study drug;
n (Baseline) = subjects who were randomized and received at least 1 dose of study drug, had Baseline and postbaseline values; Preg = pregabalin; SD = standard deviation;
SE = standard error; SF-36 = short form 36.

Table 15. SF-36 - Bodily Pain and General Health: Analysis of Covariance of the Change From Baseline at Week 6 (Observed Cases) and at the Last Observation (LOCF), ITT Population

	Bodily Pain						General Health					
	Placebo (N=23) n (%)	Preg 50 mg (N=22) n (%)	Preg 100 mg (N=23) n (%)	Preg 150 mg (N=22) n (%)	Preg 300 mg (N=24) n (%)	Preg 450 mg (N=23) n (%)	Placebo (N=23) n (%)	Preg 50 mg (N=22) n (%)	Preg 100 mg (N=23) n (%)	Preg 150 mg (N=22) n (%)	Preg 300 mg (N=24) n (%)	Preg 450 mg (N=23) n (%)
Baseline												
n	22	20	23	19	24	21	22	20	23	20	24	21
Mean	58.5	57.5	58.3	53.4	60.4	55.7	68.3	59.0	71.8	65.5	68.1	67.6
SD	25.02	23.32	22.93	23.66	23.83	22.87	21.06	16.91	21.60	23.24	27.65	24.69
Median	51.0	61.5	62.0	61.0	62.0	52.0	72.0	60.0	77.0	72.0	77.0	82.0
Minimum	22	0	20	10	0	0	25	25	35	25	15	5
Maximum	100	100	100	84	84	100	100	87	100	100	100	92
Week 6												
n	21	19	22	17	23	20	21	19	22	17	23	20
Mean	64.0	71.7	69.4	72.4	70.0	74.1	75.1	63.9	74.9	71.5	69.7	73
SD	17.1	20.99	22.91	24.93	25.54	18.76	15.72	21.63	20.26	24.33	27.51	17.14
Median	62	74	74	74	74	74	77	67	77	77	82	77
Minimum	32	31	22	22	12	41	40	20	40	30	10	27
Maximum	100	100	100	100	100	100	100	97	100	100	100	100
Change From Baseline to Week 6												
n	21	19	22	16	23	20	21	19	22	17	23	20
Mean	6.2	15.6	13	18.4	10.7	17.6	6.0	6.2	3.0	7.1	1.1	4.6
SD	22.27	18.25	25.38	28.42	17.48	25.09	13.02	17.86	10.27	14.61	12.03	18.02
Median	10.0	11.0	10.5	13.5	12.0	12.0	5.0	5.0	0.0	8.0	0.0	0.0
Minimum	-39	-10	-52	-50	-33	-28	-15	-37	-20	-12	-22	-25
Maximum	59	58	64	64	43	78	32	45	27	37	35	42
LS Mean	6.9	15.8	12.9	16.9	13.3	18.1	6.5	5.2	4.0	7.5	3.6	5.9
SE	4.16	4.41	4.07	4.87	4.17	4.31	2.81	3.05	2.75	3.15	2.82	2.9
LS Mean Difference		8.9	6.0	10.0	6.4	11.2		-1.3	-2.6	1.0	-2.9	-0.7
95% LS Mean Difference		(-3.1, 20.9)	(-5.6, 17.5)	(-2.7, 22.7)	(-5.3, 18.0)	(-0.7, 23.0)		(-9.5, 6.9)	(-10.3, 5.2)	(-7.4, 9.4)	(-10.8, 4.9)	(-8.7, 7.3)
P-value		0.1441	0.3076	0.1209	0.2791	0.0644		0.7544	0.5142	0.8158	0.4599	0.8636
Last Observation												
n	22	20	23	20	24	21	22	20	23	20	24	21
Mean	65.6	73.1	66.4	73.1	70.2	73.0	74.2	64.9	74.0	71.6	68.9	71.9
SD	18.37	21.39	26.66	23.29	24.99	18.96	15.93	21.43	20.22	23.25	27.20	17.44
Median	62.0	79.0	74.0	74.0	74.0	74.0	77.0	67.0	77.0	74.5	79.5	77.0

Table 15. SF-36 - Bodily Pain and General Health: Analysis of Covariance of the Change From Baseline at Week 6 (Observed Cases) and at the Last Observation (LOCF), ITT Population

	Bodily Pain						General Health					
	Placebo (N=23) n (%)	Preg 50 mg (N=22) n (%)	Preg 100 mg (N=23) n (%)	Preg 150 mg (N=22) n (%)	Preg 300 mg (N=24) n (%)	Preg 450 mg (N=23) n (%)	Placebo (N=23) n (%)	Preg 50 mg (N=22) n (%)	Preg 100 mg (N=23) n (%)	Preg 150 mg (N=22) n (%)	Preg 300 mg (N=24) n (%)	Preg 450 mg (N=23) n (%)
Minimum	32	31	0	22	12	41	40	20	40	30	10	27
Maximum	100	100	100	100	100	100	100	97	100	100	100	100
Change From Baseline to Last Observation												
n	22	20	23	19	24	21	22	20	23	20	24	21
Mean	7.1	15.6	8.0	18.3	9.8	17.2	5.9	5.9	2.2	6.1	0.8	4.3
SD	22.14	17.76	34.20	26.04	17.61	24.51	12.71	17.44	10.71	13.94	11.88	17.59
Median	10.5	11.5	10.0	16.0	12.0	11.0	5.0	5.0	0.0	6.0	0.0	0.0
Minimum	-39	-10	-100	-50	-33	-28	-15	-37	-20	-12	-22	-25
Maximum	59	58	64	64	43	78	32	45	27	37	35	42
LS Mean	7.7	15.7	8.5	16.0	11.7	16.3	6.2	5.0	3.1	6.5	2.4	5.1
SE	4.35	4.60	4.26	4.78	4.31	4.49	2.73	2.95	2.69	2.89	2.72	2.81
LS Mean Difference		8.0	0.8	8.3	3.9	8.6		-1.3	-3.1	0.3	-3.8	-1.1
95% LS Mean Difference		(-4.6, 20.5)	(-11.2, 12.8)	(-4.5, 21.1)	(-8.2, 16.1)	(-3.8, 21.0)		(-9.2, 6.7)	(-10.6, 4.5)	(-7.6, 8.2)	(-11.4, 3.9)	(-8.9, 6.6)
P-value		0.2101	0.8948	0.2021	0.5218	0.1728		0.7568	0.4256	0.9360	0.3289	0.7700

The LS Mean, SE, 95% CI and P-value were from an analysis of covariance (ANCOVA) with treatment and geographic region as main effects and baseline value as covariate in the model.
LS Mean Difference: Pregabalin – Placebo; SF-36: Medical Outcome Study - Short Form 36.
CI = confidence interval; ITT = intent to treat; LS Mean = least squares mean; N = subjects who were randomized and received at least 1 dose of study drug;
n (Baseline) = subjects who were randomized and received at least 1 dose of study drug, had Baseline and postbaseline values; Preg = pregabalin; SD = standard deviation;
SE = standard error; SF-36 = short form 36.

Table 16. SF-36 – Vitality and Social Functioning: Analysis of Covariance of the Change From Baseline at Week 6 (Observed Cases) and at the Last Observation (LOCF), ITT Population

	Vitality Analysis						Social Functioning Analysis					
	Placebo (N=23) n (%)	Preg 50 mg (N=22) n (%)	Preg 100 mg (N=23) n (%)	Preg 150 mg (N=22) n (%)	Preg 300 mg (N=24) n (%)	Preg 450 mg (N=23) n (%)	Placebo (N=23) n (%)	Preg 50 mg (N=22) n (%)	Preg 100 mg (N=23) n (%)	Preg 150 mg (N=22) n (%)	Preg 300 mg (N=24) n (%)	Preg 450 mg (N=23) n (%)
Baseline												
n	22	20	23	20	24	21	22	20	23	20	24	21
Mean	51.7	45.9	42.4	42.2	46.6	49.1	78.4	76.9	73.9	70.6	74.0	76.8
SD	23.95	19.58	21.32	23.90	23.53	23.49	22.55	24.09	26.09	21.94	28.05	28.85
Median	59.4	50.0	37.5	43.8	53.1	50.0	87.5	87.5	75.0	68.8	75.0	87.5
Minimum	13	13	6	0	0	6	38	13	25	25	0	0
Maximum	100	81	75	81	81	81	100	100	100	100	100	100
Week 6												
n	21	19	22	17	23	20	21	19	22	17	23	20
Mean	58.0	55.3	54.5	58.8	54.3	60.9	85.7	84.2	80.7	77.2	83.7	91.9
SD	22.46	23.13	22.09	23.08	26.14	21.35	18.66	24.24	22.73	27.33	27.29	13.62
Median	62.5	56.3	59.4	56.3	62.5	59.4	100.0	100.0	87.5	87.5	100.0	100.0
Minimum	25	6	6	13	6	13	50	25	25	25	13	63
Maximum	94	100	88	88	100	100	100	100	100	100	100	100
Change From Baseline to Week 6												
n	21	19	22	17	23	20	21	19	22	17	23	20
Mean	4.8	10.2	10.8	19.5	8.7	11.3	6.0	7.9	4.5	6.6	10.3	15.0
SD	12.01	26.20	17.80	18.07	26.16	18.65	15.62	22.52	17.91	22.15	25.74	23.51
Median	6.3	6.3	9.4	18.8	6.3	12.5	0.0	12.5	0.0	0.0	0.0	0.0
Minimum	-31	-50	-25	-6	-25	-19	-13	-38	-38	-25	-38	0
Maximum	25	75	38	50	88	44	50	63	38	50	88	75
LS Mean	7.4	11.1	9.9	18.5	11.7	13.9	7.8	8.3	4.8	4.4	9.5	15.6
SE	3.98	4.18	3.86	4.46	3.95	4.08	3.98	4.20	3.88	4.47	4.00	4.10
LS Mean Difference		3.7	2.5	11.1	4.3	6.5		0.4	-3.1	-3.4	1.6	7.8
95% LS Mean Difference		(-7.8, 15.1)	(-8.5, 13.5)	(-0.8, 23.0)	(-6.8, 15.4)	(-4.7, 17.7)		(-11.0, 11.9)	(-14.1, 7.9)	(-15.3, 8.4)	(-9.6, 12.8)	(-3.5, 19.1)
P-value		0.5281	0.6566	0.0677	0.4443	0.2543		0.9416	0.5824	0.5668	0.7769	0.1753
Last Observation												
n	22	20	23	20	24	21	22	20	23	20	24	21
Mean	55.7	55.6	52.4	59.4	53.9	60.1	83.5	84.4	77.7	78.1	83.3	91.1
SD	24.54	22.57	23.82	21.89	25.66	21.15	20.91	23.60	26.37	25.29	26.75	13.77
Median	59.4	56.3	56.3	56.3	62.5	56.3	100.0	100.0	87.5	87.5	100.0	100.0

Table 16. SF-36 – Vitality and Social Functioning: Analysis of Covariance of the Change From Baseline at Week 6 (Observed Cases) and at the Last Observation (LOCF), ITT Population

	Vitality Analysis						Social Functioning Analysis					
	Placebo (N=23) n (%)	Preg 50 mg (N=22) n (%)	Preg 100 mg (N=23) n (%)	Preg 150 mg (N=22) n (%)	Preg 300 mg (N=24) n (%)	Preg 450 mg (N=23) n (%)	Placebo (N=23) n (%)	Preg 50 mg (N=22) n (%)	Preg 100 mg (N=23) n (%)	Preg 150 mg (N=22) n (%)	Preg 300 mg (N=24) n (%)	Preg 450 mg (N=23) n (%)
Minimum	6	6	6	13	6	13	38	25	13	25	13	63
Maximum	94	100	88	88	100	100	100	100	100	100	100	100
Change From Baseline to Last Observation												
n	22	20	23	20	24	21	22	20	23	20	24	21
Mean	4.0	9.7	10.1	17.2	7.3	11.0	5.1	7.5	3.8	7.5	9.4	14.3
SD	12.28	25.61	17.75	17.78	26.50	18.21	15.74	21.99	17.85	20.84	25.6	23.15
Median	6.3	6.3	6.3	12.5	6.3	12.5	0.0	6.3	0.0	0.0	0.0	0.0
Minimum	-31	-50	-25	-6	-25	-19	-13	-38	-38	-25	-38	0
Maximum	25	75	38	50	88	44	50	63	38	50	88	75
LS Mean	5.8	10.6	8.6	16.8	9.5	12.8	6.5	8.1	3.3	5.4	8.6	14.9
SE	3.94	4.14	3.84	4.16	3.88	4.03	3.91	4.12	3.82	4.15	3.88	4.01
LS Mean Difference		4.8	2.8	11.0	3.7	7.0		1.6	-3.2	-1.1	2.0	8.3
95% LS Mean Difference		(-6.5, 16.1)	(-8.2, 13.7)	(-0.4, 22.4)	(-7.3, 14.6)	(-4.1, 18.1)		(-9.7, 12.8)	(-14.0, 7.6)	(-12.5, 10.2)	(-8.9, 12.9)	(-2.8, 19.4)
P-value		0.4019	0.6191	0.0575	0.5107	0.216		0.7851	0.5561	0.8415	0.7169	0.1392

The LS Mean, SE, 95% CI and P-value were from an analysis of covariance (ANCOVA) with treatment and geographic region as main effects and baseline value as covariate in the model.
LS Mean Difference: Pregabalin – Placebo; SF-36: Medical Outcome Study - Short Form 36.
CI = confidence interval; ITT = intent to treat; LS Mean = least squares mean; N = subjects who were randomized and received at least 1 dose of study drug;
n (Baseline) = subjects who were randomized and received at least 1 dose of study drug, had Baseline and postbaseline values; Preg = pregabalin; SD = standard deviation;
SE = standard error; SF-36 = short form 36.

Table 17. SF-36 - Role Emotional and Mental Health: Analysis of Covariance of the Change From Baseline at Week 6 (Observed Cases) and at the Last Observation (LOCF), ITT Population

	Role Emotional Analysis						Mental Health Analysis					
	Placebo (N=23) n (%)	Preg 50 mg (N=22) n (%)	Preg 100 mg (N=23) n (%)	Preg 150 mg (N=22) n (%)	Preg 300 mg (N=24) n (%)	Preg 450 mg (N=23) n (%)	Placebo (N=23) n (%)	Preg 50 mg (N=22) n (%)	Preg 100 mg (N=23) n (%)	Preg 150 mg (N=22) n (%)	Preg 300 mg (N=24) n (%)	Preg 450 mg (N=23) n (%)
Baseline												
n	22	20	23	20	24	21	22	20	23	20	24	21
Mean	80.7	77.1	70.7	78.3	80.6	70.6	71.8	67.5	59.3	65.8	70.2	65.7
SD	21.27	28.08	28.41	23.48	26.20	29.89	17.43	21.73	23.52	19.89	18.27	24.76
Median	87.5	83.3	75.0	87.5	91.7	91.7	70.0	72.5	55.0	62.5	75.0	75.0
Minimum	33	0	25	25	8	17	35	20	30	30	25	15
Maximum	100	100	100	100	100	100	100	95	95	90	90	95
Week 6												
n	21	19	22	17	23	20	21	19	22	17	23	20
Mean	77.8	82.9	82.2	78.4	86.6	86.3	72.9	67.6	66.8	73.2	72.2	77.3
SD	28.05	19.54	24.71	26.36	25.71	19.92	16.63	20.23	21.41	18.79	21.99	18.39
Median	91.7	83.3	95.8	91.7	100.0	100.0	70.0	65.0	72.5	80.0	80.0	85.0
Minimum	25	33	33	25	8	50	40	25	25	40	25	30
Maximum	100	100	100	100	100	100	95	95	95	100	100	100
Change From Baseline to Week 6												
n	21	19	22	17	23	20	21	19	22	17	23	20
Mean	-4.4	7.0	9.5	0.5	6.9	15.0	0.5	1.1	6.4	8.2	2.0	10.8
SD	18.18	26.10	20.30	25.43	17.16	23.82	16.04	19.69	13.90	18.28	20.71	20.73
Median	0.0	0.0	4.2	0.0	0.0	8.3	0.0	0.0	0.0	5.0	0.0	5.0
Minimum	-58	-33	-33	-33	-17	-17	-30	-30	-10	-30	-35	-25
Maximum	25	58	50	67	67	67	30	35	45	45	65	60
LS Mean	-2.1	6.7	7.8	1.0	8.1	12.7	2.9	1.0	3.6	7.6	3.7	10.7
SE	4.16	4.38	4.05	4.63	4.13	4.31	3.49	3.68	3.43	3.90	3.47	3.59
LS Mean Difference		8.7	9.9	3.1	10.2	14.8		-1.8	0.7	4.7	0.9	7.9
95% LS Mean Difference		(-3.2, 20.7)	(-1.6, 21.4)	(-9.2, 15.4)	(-1.4, 21.8)	(2.9, 26.7)		(-11.9, 8.2)	(-9.1, 10.5)	(-5.7, 15.1)	(-8.9, 10.6)	(-2.1, 17.8)
P-value		0.1508	0.0916	0.6222	0.0850	0.0154		0.7201	0.8875	0.3735	0.8621	0.1203
Last Observation												
n	22	20	23	20	24	21	22	20	23	20	24	21
Mean	76.5	83.8	79.7	78.3	86.1	85.7	73.0	68.5	64.6	73.3	71.9	76.7
SD	28.01	19.40	26.92	25.56	25.26	19.57	16.23	20.07	23.54	17.27	21.56	18.12
Median	91.7	87.5	91.7	87.5	100.0	100.0	72.5	67.5	70.0	75.0	77.5	85.0

Table 17. SF-36 - Role Emotional and Mental Health: Analysis of Covariance of the Change From Baseline at Week 6 (Observed Cases) and at the Last Observation (LOCF), ITT Population

	Role Emotional Analysis						Mental Health Analysis					
	Placebo (N=23) n (%)	Preg 50 mg (N=22) n (%)	Preg 100 mg (N=23) n (%)	Preg 150 mg (N=22) n (%)	Preg 300 mg (N=24) n (%)	Preg 450 mg (N=23) n (%)	Placebo (N=23) n (%)	Preg 50 mg (N=22) n (%)	Preg 100 mg (N=23) n (%)	Preg 150 mg (N=22) n (%)	Preg 300 mg (N=24) n (%)	Preg 450 mg (N=23) n (%)
Minimum	25	33	25	25	8	50	40	25	15	40	25	30
Maximum	100	100	100	100	100	100	95	95	95	100	100	100
Change From Baseline to Last Observation												
n	22	20	23	20	24	21	22	20	23	20	24	21
Mean	-4.2	6.7	9.1	0.0	5.6	15.1	1.1	1.0	5.2	7.5	1.7	11.0
SD	17.77	25.45	19.93	23.41	18.00	23.22	15.96	19.17	14.65	18.46	20.31	20.22
Median	0.0	0.0	0.0	0.0	0.0	8.3	0.0	0.0	0.0	2.5	0.0	5.0
Minimum	-58	-33	-33	-33	-25	-17	-30	-30	-20	-30	-35	-25
Maximum	25	58	50	67	67	67	30	35	45	45	65	60
LS Mean	-2.4	6.8	6.8	0.6	6.9	12.6	3.4	1.3	2.0	7.0	3.1	10.5
SE	4.00	4.22	3.92	4.22	3.95	4.14	3.41	3.58	3.35	3.59	3.35	3.49
LS Mean Difference		9.2	9.2	3.0	9.3	15.1		-2.1	-1.4	3.7	-0.2	7.1
95% LS Mean Difference		(-2.3, 20.7)	(-1.9, 20.3)	(-8.5, 14.6)	(-1.8, 20.5)	(3.6, 26.5)		(-11.9, 7.7)	(-10.9, 8.2)	(-6.2, 13.5)	(-9.7, 9.2)	(-2.6, 16.8)
P-value		0.1163	0.1035	0.6019	0.1001	0.0103		0.6788	0.7774	0.4601	0.9611	0.1481

The LS Mean, SE, 95% CI and P-value were from an analysis of covariance (ANCOVA) with treatment and geographic region as main effects and baseline value as covariate in the model.
LS Mean Difference: Pregabalin – Placebo; SF-36: Medical Outcome Study - Short Form 36.
CI = confidence interval; ITT = intent to treat; LS Mean = least squares mean; N = subjects who were randomized and received at least 1 dose of study drug;
n (Baseline) = subjects who were randomized and received at least 1 dose of study drug, had Baseline and postbaseline values; Preg = pregabalin; SD = standard deviation;
SE = standard error; SF-36 = short form 36.

Table 18. SF-36 - Summary Physical Score and Summary Emotional Score: Analysis of Covariance of the Change From Baseline at Week 6 (Observed Cases) and at the Last Observation (LOCF), ITT Population

	Summary Physical Score Analysis						Summary Emotional Score Analysis					
	Placebo (N=23) n (%)	Preg 50 mg (N=22) n (%)	Preg 100 mg (N=23) n (%)	Preg 150 mg (N=22) n (%)	Preg 300 mg (N=24) n (%)	Preg 450 mg (N=23) n (%)	Placebo (N=23) n (%)	Preg 50 mg (N=22) n (%)	Preg 100 mg (N=23) n (%)	Preg 150 mg (N=22) n (%)	Preg 300 mg (N=24) n (%)	Preg 450 mg (N=23) n (%)
Baseline												
n	22	20	23	19	24	21	22	20	23	20	24	21
Mean	70.0	68.5	70.8	70.3	71.5	68.7	70.7	66.8	61.6	64.2	67.8	65.6
SD	20.44	15.43	17.20	18.55	20.88	20.58	18.14	20.31	22.45	17.69	22.23	23.86
Median	69.5	71.8	73.3	74.8	77.5	74.8	70.1	71.8	65.0	60.9	75.2	68.1
Minimum	25	34	36	30	15	23	44	21	22	39	12	9
Maximum	99	89	100	96	95	94	98	94	93	93	93	93
Week 6												
n	21	19	22	17	23	20	21	19	22	17	23	20
Mean	75.0	74.8	77.5	77.3	75.0	78.7	73.6	72.5	71.1	71.9	74.2	79.1
SD	17.38	17.96	16.61	21.53	23.83	14.73	17.19	19.19	20.78	21.65	23.45	16.31
Median	78.8	76.6	82.1	86.2	84.0	82.2	77.2	78.8	79.5	79.4	83.1	84.6
Minimum	35	29	42	27	13	42	43	25	29	31	16	42
Maximum	96	99	100	100	100	100	96	99	94	97	100	100
Change From Baseline to Week 6												
n	21	19	22	16	23	20	21	19	22	17	23	20
Mean	4.2	7.3	6.5	7.5	3.7	9.1	1.7	6.5	7.8	8.7	7.0	13
SD	12.29	13.78	10.06	22.35	10.36	15.43	9.69	20.48	13.10	16.98	20.83	18.82
Median	3.4	5.0	5.1	7.4	3.8	5.7	0.0	2.6	6.3	1.6	3.1	4.6
Minimum	-12	-23	-15	-49	-19	-27	-19	-35	-18	-13	-26	-5
Maximum	28	39	31	56	31	43	20	41	33	44	77	61
LS Mean	4.5	7.4	6.7	8.2	5.6	9.7	3.7	6.9	6.7	8.2	8.5	13.5
SE	2.83	3.02	2.77	3.29	2.85	2.94	3.33	3.51	3.24	3.72	3.32	3.43
LS Mean Difference		2.8	2.2	3.7	1.0	5.2		3.2	3.0	4.4	4.8	9.7
95% LS Mean Difference		(-5.4, 11.0)	(-5.6, 10.1)	(-4.9, 12.3)	(-6.9, 9.0)	(-2.9, 13.2)		(-6.4, 12.8)	(-6.3, 12.2)	(-5.5, 14.4)	(-4.5, 14.1)	(0.3, 19.2)
P-value		0.4966	0.5776	0.3955	0.7994	0.2073		0.5148	0.5255	0.3793	0.312	0.0442
Last Observation												
n	22	20	23	20	24	21	22	20	23	20	24	21
Mean	74.5	75.5	76.1	77.9	74.9	77.6	72.2	73.1	68.6	72.3	73.8	78.4
SD	17.16	17.81	17.41	20.40	23.31	15.15	18.07	18.84	23.46	20.20	23.02	16.21
Median	78.3	79.8	81.4	85.3	83.1	82.0	76.4	78.8	77.5	79.3	82.2	84.4

Table 18. SF-36 - Summary Physical Score and Summary Emotional Score: Analysis of Covariance of the Change From Baseline at Week 6 (Observed Cases) and at the Last Observation (LOCF), ITT Population

	Summary Physical Score Analysis						Summary Emotional Score Analysis					
	Placebo (N=23) n (%)	Preg 50 mg (N=22) n (%)	Preg 100 mg (N=23) n (%)	Preg 150 mg (N=22) n (%)	Preg 300 mg (N=24) n (%)	Preg 450 mg (N=23) n (%)	Placebo (N=23) n (%)	Preg 50 mg (N=22) n (%)	Preg 100 mg (N=23) n (%)	Preg 150 mg (N=22) n (%)	Preg 300 mg (N=24) n (%)	Preg 450 mg (N=23) n (%)
Minimum	35	29	42	27	13	42	42	25	15	31	16	42
Maximum	96	99	100	100	100	100	96	99	94	97	100	100
Change From Baseline to Last Observation												
n	22	20	23	19	24	21	22	20	23	20	24	21
Mean	4.4	7.1	5.3	7.0	3.4	8.9	1.5	6.2	7.0	8.0	6.0	12.8
SD	12.03	13.45	11.48	20.47	10.23	15.05	9.50	19.99	13.31	15.94	20.94	18.36
Median	4.3	4.7	5.1	6.4	2.9	5.8	-0.3	1.3	6.3	1.6	3.0	5.2
Minimum	-12	-23	-22	-49	-19	-27	-19	-35	-18	-13	-26	-5
Maximum	28	39	31	56	31	43	20	41	33	44	77	61
LS Mean	4.4	7.2	5.4	7.7	4.7	9.0	3.0	6.8	5.4	7.7	7.2	12.9
SE	2.75	2.92	2.69	3.00	2.74	2.84	3.25	3.42	3.18	3.43	3.21	3.33
LS Mean Difference		2.8	1.0	3.3	0.3	4.6		3.7	2.4	4.7	4.1	9.8
95% LS Mean Difference		(-5.2, 10.7)	(-6.6, 8.6)	(-4.7, 11.4)	(-7.4, 8.0)	(-3.2, 12.5)		(-5.6, 13.1)	(-6.6, 11.4)	(-4.7, 14.1)	(-4.9, 13.2)	(0.6, 19.1)
P-value		0.4887	0.7956	0.4148	0.9333	0.2447		0.4310	0.6001	0.3260	0.3689	0.0367

The LS Mean, SE, 95% CI and P-value were from an analysis of covariance (ANCOVA) with treatment and geographic region as main effects and baseline value as covariate in the model.
LS Mean Difference: Pregabalin – Placebo; SF-36: Medical Outcome Study - Short Form 36.
CI = confidence interval; ITT = intent to treat; LS Mean = least squares mean; N = subjects who were randomized and received at least 1 dose of study drug;
n (Baseline) = subjects who were randomized and received at least 1 dose of study drug, had baseline and postbaseline values; Preg = pregabalin; SD = standard deviation;
SE = standard error; SF-36 = short form 36.

Table 19. SF-36 - Self-Evaluated: Summary of the Change in Health Status at Baseline, Week 6 (Observed Cases) and at the Last Observation (LOCF), ITT Population

Health Status	Placebo (N=23) n (%)	Pregabalin 50 mg (N=22) n (%)	Pregabalin 100 mg (N=23) n (%)	Pregabalin 150 mg (N=22) n (%)	Pregabalin 300 mg (N=24) n (%)	Pregabalin 450 mg (N=23) n (%)
Baseline						
N assessed	22	20	23	20	24	21
Much worse now than 1 year ago	0 (0.0)	3 (15.0)	1 (4.3)	2 (10.0)	3 (12.5)	2 (9.5)
Somewhat worse now than 1 year ago	4 (18.2)	6 (30.0)	3 (13.0)	4 (20.0)	1 (4.2)	3 (14.3)
About the same as 1 year ago	15 (68.2)	9 (45.0)	15 (65.2)	14 (70.0)	14 (58.3)	12 (57.1)
Somewhat better now than 1 year ago	2 (9.1)	1 (5.0)	3 (13.0)	0 (0.0)	5 (20.8)	2 (9.5)
Much better now than 1 year ago	1 (4.5)	1 (5.0)	1 (4.3)	0 (0.0)	1 (4.2)	2 (9.5)
Week 6						
N assessed	21	19	22	17	23	20
Much worse now than 1 year ago	1 (4.8)	0 (0.0)	0 (0.0)	0 (0.0)	2 (8.7)	0 (0.0)
Somewhat worse now than 1 year ago	2 (9.5)	3 (15.8)	2 (9.1)	4 (23.5)	3 (13.0)	1 (5.0)
About the same as 1 year ago	11 (52.4)	12 (63.2)	10 (45.5)	11 (64.7)	12 (52.2)	10 (50.0)
Somewhat better now than 1 year ago	4 (19.0)	2 (10.5)	4 (18.2)	1 (5.9)	4 (17.4)	5 (25.0)
Much better now than 1 year ago	3 (14.3)	2 (10.5)	6 (27.3)	1 (5.9)	2 (8.7)	4 (20.0)
P-value		0.4452	0.4342	0.0942	0.1873	0.4709
Last Observation						
N assessed	22	20	23	20	24	21
Much worse now than 1 year ago	1 (4.5)	0 (0.0)	0 (0.0)	0 (0.0)	2 (8.3)	0 (0.0)
Somewhat worse now than 1 year ago	3 (13.6)	3 (15.0)	3 (13.0)	4 (20.0)	4 (16.7)	1 (4.8)
About the same as 1 year ago	11 (50.0)	12 (60.0)	10 (43.5)	14 (70.0)	12 (50.0)	11 (52.4)
Somewhat better now than 1 year ago	4 (18.2)	3 (15.0)	4 (17.4)	1 (5.0)	4 (16.7)	5 (23.8)
Much better now than 1 year ago	3 (13.6)	2 (10.0)	6 (26.1)	1 (5.0)	2 (8.3)	4 (19.0)
P-value		0.7118	0.4541	0.1284	0.1636	0.4291

Cochran-Mantel-Haenszel (CHM) test for difference; p-value was adjusted for geographic region at each visit.
ITT = intent-to-treat; N = number of subjects in a treatment group; n = number of subjects with SF-36 self-evaluation of health status; SF-36 = Medical Outcomes Study - Short Form 36.

Safety Results:

A summary of treatment-emergent all-causality and treatment-related AEs is provided in Table 20.

Table 20. Treatment-Emergent All-Causality and Treatment-Related Adverse Events

Number of Subjects	Placebo (N=23)	Pregabalin 50 mg (N=22)	Pregabalin 100 mg (N=23)	Pregabalin 150 mg (N=22)	Pregabalin 300 mg (N=24)	Pregabalin 450 mg (N=23)
Subjects evaluable for AEs	23	22	23	22	24	23
Number of AEs	32 (21)	25 (16)	22 (12)	55 (47)	49 (34)	48 (36)
Subjects with AEs	13 (8)	10 (8)	12 (8)	15 (11)	17 (14)	19 (16)
Subjects with SAEs	0	1	0	0	0	0
Subjects with severe AEs	1	2	3 (2)	2 (1)	3 (2)	0
Subjects discontinued due to AEs	1 (1)	2 (1)	0	5 (5)	1 (1)	2 (2)
Subjects with dose reduced or temporary discontinuation due to AEs	0	0	0	0	0	1

AE and SAE results are not separated out.
All-causality AEs are included outside of parentheses and treatment-related AEs are provided in parentheses.
AE = adverse event; N = number of subjects; SAE = serious adverse event.

Treatment-emergent all-causality non-serious AEs are presented in Table 21.

Table 21. Treatment-Emergent Non-Serious Adverse Events (All Causalities)

Number (%) of Subjects with Adverse Events by: System Organ Class and MedDRA (v11.1) Preferred Term	Placebo (N=23)	Pregabalin 50 mg (N=22)	Pregabalin 100 mg (N=23)	Pregabalin 150 mg (N=22)	Pregabalin 300 mg (N=24)	Pregabalin 450 mg (N=23)
With AEs	13 (56.5)	9 (40.9)	12 (52.2)	15 (68.2)	17 (70.8)	19 (82.6)
Blood and lymphatic system disorders	0	1 (4.5)	0	0	0	0
Thrombocytopenia	0	1 (4.5)	0	0	0	0
Ear and labyrinth disorders	0	0	0	1 (4.5)	1 (4.2)	0
Vertigo	0	0	0	1 (4.5)	1 (4.2)	0
Eye disorders	1 (4.3)	0	0	2 (9.1)	2 (8.3)	2 (8.7)
Diplopia	0	0	0	0	1 (4.2)	0
Eyelid oedema	1 (4.3)	0	0	0	0	0
Vision blurred	0	0	0	2 (9.1)	1 (4.2)	2 (8.7)
Gastrointestinal disorders	1 (4.3)	3 (13.6)	2 (8.7)	5 (22.7)	6 (25.0)	3 (13.0)
Abdominal distension	0	1 (4.5)	0	1 (4.5)	0	0
Abdominal pain upper	0	0	1 (4.3)	0	0	0
Anal fissure	0	0	1 (4.3)	0	0	0
Constipation	0	0	1 (4.3)	1 (4.5)	2 (8.3)	0
Diarrhoea	0	1 (4.5)	0	0	1 (4.2)	0
Dry mouth	0	0	0	1 (4.5)	3 (12.5)	2 (8.7)
Flatulence	0	1 (4.5)	0	0	0	0
Haemorrhoids	0	0	1 (4.3)	0	0	0
Lip swelling	0	0	0	0	0	1 (4.3)
Nausea	1 (4.3)	1 (4.5)	0	2 (9.1)	0	0
Toothache	0	0	0	1 (4.5)	0	0
Vomiting	0	0	0	0	1 (4.2)	0
General disorders and administration site conditions	3 (13.0)	1 (4.5)	4 (17.4)	4 (18.2)	7 (29.2)	6 (26.1)
Chest discomfort	1 (4.3)	0	0	0	0	0
Chills	0	1 (4.5)	0	0	1 (4.2)	0
Fatigue	0	0	4 (17.4)	2 (9.1)	1 (4.2)	2 (8.7)
Feeling abnormal	1 (4.3)	0	0	0	2 (8.3)	1 (4.3)
Feeling drunk	0	0	0	0	1 (4.2)	2 (8.7)
Feeling jittery	0	0	0	1 (4.5)	0	0
Feeling of relaxation	0	0	0	0	1 (4.2)	0
Gait disturbance	0	0	0	1 (4.5)	1 (4.2)	1 (4.3)
Hangover	0	0	0	0	0	1 (4.3)
Mucosal dryness	1 (4.3)	0	0	0	0	0

Table 21. Treatment-Emergent Non-Serious Adverse Events (All Causalities)

Number (%) of Subjects with Adverse Events by: System Organ Class and MedDRA (v11.1) Preferred Term	Placebo (N=23)	Pregabalin 50 mg (N=22)	Pregabalin 100 mg (N=23)	Pregabalin 150 mg (N=22)	Pregabalin 300 mg (N=24)	Pregabalin 450 mg (N=23)
Oedema peripheral	1 (4.3)	0	0	0	0	0
Thirst	0	0	0	1 (4.5)	0	0
Infections and infestations	3 (13.0)	3 (13.6)	1 (4.3)	2 (9.1)	5 (20.8)	3 (13.0)
Bronchitis	0	0	0	0	0	1 (4.3)
Cystitis	1 (4.3)	0	0	0	0	0
Fungal infection	0	1 (4.5)	0	0	0	0
Gastroenteritis viral	0	0	0	0	1 (4.2)	0
Influenza	0	0	0	0	1 (4.2)	0
Kidney infection	0	0	0	1 (4.5)	0	0
Lower respiratory tract infection	1 (4.3)	0	0	0	0	0
Nasopharyngitis	0	0	1 (4.3)	0	1 (4.2)	1 (4.3)
Pharyngitis streptococcal	0	0	0	0	0	1 (4.3)
Respiratory tract infection	0	0	0	0	0	1 (4.3)
Sinusitis	0	1 (4.5)	0	1 (4.5)	1 (4.2)	0
Upper respiratory tract infection	1 (4.3)	1 (4.5)	0	0	2 (8.3)	0
Urinary tract infection	0	1 (4.5)	0	0	0	0
Investigations	3 (13.0)	1 (4.5)	0	2 (9.1)	0	3 (13.0)
Aspartate aminotransferase increased	0	0	0	1 (4.5)	0	0
Blood creatine phosphokinase increased	0	0	0	0	0	1 (4.3)
Blood pressure increased	1 (4.3)	0	0	0	0	0
Blood thyroid stimulating hormone increased	1 (4.3)	0	0	0	0	0
Creatinine renal clearance increased	0	0	0	1 (4.5)	0	0
Mean cell volume increased	0	0	0	1 (4.5)	0	0
Transaminases increased	0	0	0	0	0	1 (4.3)
Weight increased	1 (4.3)	0	0	1 (4.5)	0	1 (4.3)
White blood cell count decreased	0	1 (4.5)	0	0	0	0
Metabolism and nutrition disorders	0	0	0	1 (4.5)	0	1 (4.3)
Hypoglycaemia	0	0	0	0	0	1 (4.3)
Increased appetite	0	0	0	1 (4.5)	0	0
Musculoskeletal and connective tissue disorders	0	1 (4.5)	1 (4.3)	2 (9.1)	3 (12.5)	2 (8.7)
Arthralgia	0	0	0	1 (4.5)	1 (4.2)	0
Back pain	0	0	0	0	1 (4.2)	1 (4.3)
Joint swelling	0	1 (4.5)	0	1 (4.5)	0	0

Table 21. Treatment-Emergent Non-Serious Adverse Events (All Causalities)

Number (%) of Subjects with Adverse Events by: System Organ Class and MedDRA (v11.1) Preferred Term	Placebo (N=23)	Pregabalin 50 mg (N=22)	Pregabalin 100 mg (N=23)	Pregabalin 150 mg (N=22)	Pregabalin 300 mg (N=24)	Pregabalin 450 mg (N=23)
Muscle spasms	0	0	1 (4.3)	0	0	0
Muscular weakness	0	0	0	1 (4.5)	0	0
Myalgia	0	0	0	0	0	1 (4.3)
Pain in extremity	0	1 (4.5)	0	1 (4.5)	1 (4.2)	0
Tendonitis	0	0	0	1 (4.5)	0	0
Nervous system disorders	6 (26.1)	5 (22.7)	7(30.4)	10 (45.5)	8 (33.3)	13 (56.5)
Amnesia	1 (4.3)	0	0	0	0	0
Depressed level of consciousness	0	0	0	1 (4.5)	0	0
Disturbance in attention	1 (4.3)	0	0	1 (4.5)	0	1 (4.3)
Dizziness	1 (4.3)	0	2 (8.7)	5 (22.7)	2 (8.3)	7 (30.4)
Dyslalia	0	0	0	1 (4.5)	0	1 (4.3)
Headache	3(13.0)	5 (22.7)	2 (8.7)	2 (9.1)	4 (16.7)	2 (8.7)
Hypoaesthesia	0	0	0	0	0	1 (4.3)
Hypokinesia	0	0	0	1 (4.5)	0	0
Lethargy	0	0	0	1 (4.5)	0	1 (4.3)
Paraesthesia	1 (4.3)	0	1 (4.3)	0	0	1 (4.3)
Post-traumatic headache	1 (4.3)	0	0	0	0	0
Restless legs syndrome	0	1 (4.5)	0	0	0	0
Sciatica	0	0	1 (4.3)	0	0	0
Sedation	2 (8.7)	0	0	1 (4.5)	0	1 (4.3)
Sinus headache	0	0	0	0	0	1 (4.3)
Somnolence	1 (4.3)	0	1 (4.3)	6 (27.3)	6 (25.0)	5 (21.7)
Tunnel vision	0	0	0	0	1 (4.2)	0
Psychiatric disorders	5 (21.7)	2 (9.1)	1 (4.3)	2 (9.1)	2 (8.3)	2 (8.7)
Abnormal dreams	3 (13.0)	0	0	0	0	0
Anxiety	0	1 (4.5)	0	0	0	0
Confusional state	0	0	0	1 (4.5)	0	0
Depression	1 (4.3)	0	0	1 (4.5)	0	0
Disorientation	0	1 (4.5)	0	0	0	0
Elevated mood	0	0	0	0	0	1 (4.3)
Euphoric mood	0	0	0	0	1 (4.2)	0
Libido decreased	0	0	0	0	1 (4.2)	1 (4.3)
Nervousness	0	0	0	1 (4.5)	0	0

Table 21. Treatment-Emergent Non-Serious Adverse Events (All Causalities)

Number (%) of Subjects with Adverse Events by: System Organ Class and MedDRA (v11.1) Preferred Term	Placebo (N=23)	Pregabalin 50 mg (N=22)	Pregabalin 100 mg (N=23)	Pregabalin 150 mg (N=22)	Pregabalin 300 mg (N=24)	Pregabalin 450 mg (N=23)
Nightmare	0	0	1 (4.3)	0	0	0
Restlessness	1 (4.3)	0	0	0	0	0
Stress	1 (4.3)	0	0	0	0	0
Renal and urinary disorders	0	0	0	0	0	1 (4.3)
Urinary incontinence	0	0	0	0	0	1 (4.3)
Reproductive system and breast disorders	0	1 (4.5)	2 (8.7)	0	0	1 (4.3)
Erectile dysfunction	0	0	1 (4.3)	0	0	1 (4.3)
Postmenopausal haemorrhage	0	1 (4.5)	0	0	0	0
Prostatitis	0	0	1 (4.3)	0	0	0
Respiratory, thoracic and mediastinal disorders	0	1 (4.5)	0	2 (9.1)	3 (12.5)	1 (4.3)
Epistaxis	0	1 (4.5)	0	0	0	0
Nasal congestion	0	0	0	1 (4.5)	2 (8.3)	0
Oropharyngeal pain	0	0	0	1 (4.5)	1 (4.2)	1 (4.3)
Rhinitis allergic	0	0	0	0	1 (4.2)	0
Snoring	0	0	0	1 (4.5)	1 (4.2)	0
Skin and subcutaneous tissue disorders	1 (4.3)	1 (4.5)	2 (8.7)	2 (9.1)	1 (4.2)	0
Dry skin	0	0	1 (4.3)	0	0	0
Photosensitivity reaction	0	0	0	1 (4.5)	0	0
Pruritus	0	1 (4.5)	1 (4.3)	1 (4.5)	1 (4.2)	0
Rash	1 (4.3)	0	0	0	0	0
Surgical and medical procedures	1 (4.3)	0	0	0	0	0
Tooth extraction	1 (4.3)	0	0	0	0	0
Vascular disorders	1 (4.3)	0	0	2 (9.1)	1 (4.2)	0
Hot flush	1 (4.3)	0	0	2 (9.1)	1 (4.2)	0
Hypotension	0	0	0	0	1 (4.2)	0

Subjects were only counted once per treatment for each row. Included data up to 999 days after last dose of study drug.
MedDRA (v11.1) coding dictionary applied.
MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects; v = version.

A summary of the incidence of treatment-related AEs is provided in Table 22.

Table 22. Treatment-Related Treatment-Emergent Adverse Events Experienced by at Least 2 Total Subjects

MedDRA (v11.1) Preferred Term	Placebo (N=23) n (%)	Pregabalin 50 mg (N=22) n (%)	Pregabalin 100 mg (N=23) n (%)	Pregabalin 150 mg (N=22) n (%)	Pregabalin 300 mg (N=24) n (%)	Pregabalin 450 mg (N=23) n (%)
Subjects with AEs	8	8	8	11	14	16
Dizziness	1 (4.3)	0	2 (8.7)	5 (22.7)	2 (8.3)	6 (26.1)
Somnolence	1 (4.3)	0	1 (4.3)	6 (27.3)	6 (25.0)	5 (21.7)
Dry mouth	0	0	0	1 (4.5)	3 (12.5)	2 (8.7)
Fatigue	0	0	3 (13.0)	2 (9.1)	1 (4.2)	2 (8.7)
Feeling drunk	0	0	0	0	1 (4.2)	2 (8.7)
Vision blurred	0	0	0	2 (9.1)	1 (4.2)	2 (8.7)
Disturbance in attention	1 (4.3)	0	0	1 (4.5)	0	1 (4.3)
Dyslalia	0	0	0	1 (4.5)	0	1 (4.3)
Erectile dysfunction	0	0	1 (4.3)	0	0	1 (4.3)
Feeling abnormal	1 (4.3)	0	0	0	2 (8.3)	1 (4.3)
Gait disturbance	0	0	0	1 (4.5)	1 (4.2)	1 (4.3)
Headache	1 (4.3)	5 (22.7)	1 (4.3)	2 (9.1)	3 (12.5)	1 (4.3)
Lethargy	0	0	0	1 (4.5)	0	1 (4.3)
Libido decreased	0	0	0	0	1 (4.2)	1 (4.3)
Paresthesia	1 (4.3)	0	1 (4.3)	0	0	1 (4.3)
Sedation	2 (8.7)	0	0	1 (4.5)	0	1 (4.3)
Weight increased	1 (4.3)	0	0	1 (4.5)	0	1 (4.3)
Abdominal distension	0	1 (4.5)	0	1 (4.5)	0	0
Abnormal dreams	3 (13.0)	0	0	0	0	0
Arthralgia	0	0	0	1 (4.5)	1 (4.2)	0
Constipation	0	0	0	1 (4.5)	2 (8.3)	0
Depression	1 (4.3)	0	0	1 (4.5)	0	0
Hot flush	1 (4.3)	0	0	1 (4.5)	1 (4.2)	0
Joint swelling	0	1 (4.5)	0	1 (4.5)	0	0
Nausea	1 (4.3)	1 (4.5)	0	2 (9.1)	0	0
Pain in extremity	0	1 (4.5)	0	1 (4.5)	0	0
Vertigo	0	0	0	1 (4.5)	1 (4.2)	0

AE and SAE results are not separated out.
AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects in treatment group; n = number of subject; SAE = serious adverse event; v = version.

Serious Adverse Events (SAEs): One subject reported a treatment-emergent SAE (gastric cancer in a pregabalin 50 mg subject that was not considered related to study drug) and was discontinued from the study due to the event. Treatment-emergent SAEs (all causalities) are presented in Table 23.

Table 23. Treatment-Emergent Serious Adverse Events by Special Organ Class and Preferred Term (All Causalities)

Number (%) of Subjects with Adverse Events by: System Organ Class and MedDRA (v11.1) Preferred Term	Placebo (N=23) n (%)	Pregabalin 50 mg (N=22) n (%)	Pregabalin 100 mg (N=23) n (%)	Pregabalin 150 mg (N=22) n (%)	Pregabalin 300 mg (N=24) n (%)	Pregabalin 450 mg (N=23) n (%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	1 (4.5)	0	0	0	0
Gastric cancer	0	1 (4.5)	0	0	0	0

Subjects were only counted once per treatment for each row. Included data up to 999 days after last dose of study drug. MedDRA (v11.1) coding dictionary applied.
MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects in treatment group; n = number of subject; v = version.

There were no deaths during the study.

Permanent Discontinuations due to AEs: A total of 11/137 (8.0%) subjects permanently discontinued the study due to an AE (1 placebo subject; 2 pregabalin 50 mg subjects; 5 pregabalin 150 mg subjects; 1 pregabalin 300 mg subject; and 2 pregabalin 450 mg subjects). Discontinuations due to AEs are summarized in Table 24.

Table 24. Discontinuations Due to Adverse Events

Serial Number	System Organ Class	Adverse Event (MedDRA Preferred Term)	Start Day[a]	Stop Day[a]	Severity	Outcome	Study Drug Action	Causality	SAE
Placebo									
1	Psychiatric disorders	Restlessness	26	>29	Moderate	Still present	Permanently discontinued	Study drug	No
Pregabalin 50 mg/day									
2	Nervous system disorders	Headache	11	22	Moderate	Resolved	Permanently discontinued	Study drug	No
3	Neoplasms benign, malignant, and unspecified (Incl Cysts and Polyps)	Gastric cancer	13	30	Severe	Resolved	Permanently discontinued	Other-unknown	Yes
Pregabalin 150 mg/day									
4	Nervous system disorders	Disturbance in attention	4	12	Severe	Resolved	Permanently discontinued	Study drug	No
		Dyslalia	3	9	Moderate	Resolved	Permanently discontinued	Study drug	No
		Hypokinesia	4	12	Moderate	Resolved	Permanently discontinued	Study drug	No
5	Psychiatric disorders	Depression	27	31	Moderate	Resolved	Permanently discontinued	Study drug	No
6	Eye disorders	Vision blurred	6	9	Mild	Resolved	Permanently discontinued	Study drug	No
	General disorders and administration site disorders	Feeling jittery	6	9	Mild	Resolved	Permanently discontinued	Study drug	No
	Nervous system disorders	Dizziness	6	9	Mild	Resolved	Permanently discontinued	Study drug	No
7	Eye disorders	Vision blurred	25	31	Moderate	Resolved	Permanently discontinued	Study drug	No
	Gastrointestinal Disorders	Nausea	25	31	Moderate	Resolved	Permanently discontinued	Study drug	No
	Nervous system disorders	Dizzines	25	31	Moderate	Resolved	Permanently discontinued	Study drug	No
8	Ear and labyrinth disorders	Vertigo	1	9	Moderate	Resolved	Permanently discontinued	Study drug	No
Pregabalin 300 mg/day									
9	General disorders and administration site conditions	Feeling abnormal	2	10	Severe	Resolved	Permanently discontinued	Study drug	No

Table 24. Discontinuations Due to Adverse Events

Serial Number	System Organ Class	Adverse Event (MedDRA Preferred Term)	Start Day[a]	Stop Day[a]	Severity	Outcome	Study Drug Action	Causality	SAE
Pregabalin 450 mg/day									
10	General disorders and administration site conditions	Gait disturbance	7	20	Moderate	Resolved	Permanently discontinued	Study drug	No
11	Nervous system disorders	Dizziness	2	8	Mild	Resolved	Permanently discontinued	Study drug	No

MedDRA (v11.1) coding dictionary applied.
MedDRA = Medical Dictionary for Regulatory Activities; SAE = serious adverse event.
a. Day relative to start of study treatment. First day of study treatment = Day 1.

Temporary Discontinuation due to AEs: One subject (1 of 137; 0.7%) from the pregabalin 450 mg group required a temporary discontinuation due to an AE. The subject had mild nasopharyngitis on Day 25, which resolved on Day 27. The AE was not considered related to study drug. The subject missed the Day 24 and Day 25 pregabalin doses due to this AE.

Overall, the incidences of laboratory abnormalities in subjects with a normal Baseline, abnormal Baseline, and without regards to Baseline abnormality were similar among treatment groups. There were no clinically meaningful differences among treatment groups in the median changes from Baseline to the last observation. There did not appear to be a dose-related effect of pregabalin on vital sign parameters including orthostatic changes in blood pressure. No subject had a corrected QT interval (QTc), QTcB, or QTcF value >500 msec during the study. Overall, there did not appear to be any untoward effects of pregabalin on ECG parameters.

CONCLUSIONS:

- A dose-response for pregabalin was observed and well characterized for the Week 6 change from Baseline in IRLS total score. The results from the dose-response analysis estimated the median ED90 based on a bootstrap distribution is 123.9 mg/day.

- Pregabalin, administered at doses of 50 mg/day to 450 mg/day for 6 weeks in subjects with RLS, was safe and well tolerated with a low incidence of SAEs, discontinuations due to AEs, and severe AEs. The incidence of AEs tended to increase with dose. The most common treatment-related AEs in this study were dizziness and somnolence, both of which were observed predominantly at doses of 150 mg/day and higher.

- Decreases in mean IRLS total score change from Baseline indicating improvement in symptoms, were observed at Week 1 for all pregabalin treatment groups. Further decreases in mean IRLS were generally observed for all treatments out to Week 6 and these decreases were more evident at doses of 150 mg/day and higher.

- The highest percentage of CGI-I responders was observed at the last visit for subjects who received pregabalin 300 and 450 mg/day compared with subjects who received placebo or lower doses of pregabalin.

- There was a suggested dose-response relationship between subjective perception of sleep and pregabalin dose, as there did appear to be an increase in sleep quality with increased pregabalin doses.

- There were improvements in quality of life, as measured by the RLS-QoL for placebo and pregabalin groups; however, there did not appear to be a dose-response relationship or a large difference between pregabalin groups and placebo.

- Discontinuations due to AEs (all causality) tended to be higher at higher pregabalin doses (eg, 150 and 450 mg/day doses) and suggested a dose-response relationship for this finding.

- The exploratory actigraphy data suggested noticeable improvement in sleep, as demonstrated by a significant increase in total sleep time and a decrease in interrupted sleep in pregabalin compared to placebo at Week 6.