PFIZER INC.

These results are supplied for informational purposes only.
Prescribing decisions should be made based on the approved package insert.

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

PROTOCOL NO.: A0081186

PROTOCOL TITLE: Randomized, Double-Blind, 12-Month Study of Pregabalin in Subjects With Restless Legs Syndrome

Study Centers: Ninety-five (95) centers took part in the study and randomized subjects: 37 in the United States (US), 36 in Germany, 5 each in Spain and Sweden, 4 each in Finland and Italy, 3 in Austria, and 1 in the United Kingdom (UK).

Study Initiation Date and Final Completion Date: 23 December 2008 to 28 April 2011

Phase of Development: Phase 3

Study Objectives:

Primary Objectives:

- To assess efficacy of pregabalin during the first 12-week treatment in subjects with restless leg syndrome (RLS) as compared to placebo;
- To compare the rate of augmentation of pregabalin to doses of pramipexole over 9 or 12 months in subjects with RLS.

Secondary Objectives:

- To assess the comparability of efficacy of pregabalin and pramipexole in treating symptoms of RLS with pregabalin or pramipexole during the first 12 weeks and beyond, through end of the study;
- To assess the severity of augmentation associated with pregabalin or pramipexole treatment;
- To assess the tolerability and safety of pregabalin and pramipexole treatment over 1 year;
- To assess the impact of pregabalin and pramipexole treatment on subjective sleep parameters over 1 year;

- To assess the impact of pregabalin and pramipexole treatment on next-day impact (NDI) over 1 year;
- To assess the impact of pregabalin and pramipexole treatment on mood as compared to placebo during the first 12 weeks;
- To assess the impact of pregabalin and pramipexole treatment on quality of life (QoL) over 1 year;
- To assess the impact of pregabalin and pramipexole treatment on limb pain during the first 12 weeks;
- To assess the impact of pregabalin and pramipexole treatment on work productivity and activity impairment over 1 year.

METHODS

Study Design: This was a fixed-dose, randomized, 12-week, placebo-controlled, double-blind study, with a comparator-controlled component that assessed pregabalin and pramipexole tolerability and safety over a total of 52 weeks. The study provided pivotal efficacy data for pregabalin over an initial 12-week period that assessed the alleviation of RLS symptoms by study drug in these subjects. In addition, pregabalin efficacy was evaluated by rate of efficacy augmentation, time to efficacy augmentation, and general tolerability and safety of pregabalin and pramipexole in subjects with moderate to severe idiopathic RLS over 52 weeks.

Active treatments included fixed dose 300 mg/day pregabalin and 0.25 mg/day (or 0.5 mg/day) pramipexole. Each active treatment was administered over a 2-week escalation period for a total study duration of 52 weeks. Subjects who were initially randomized to placebo were redistributed to 1 of these active treatment arms after 12 weeks, and continued study treatment for the remaining 40 weeks. At the end of the 52-week, double-blind treatment period, there was a 1-week study drug taper-down period. The schedule of activities is summarized in Table 1.

Table 1. Schedule of Activities

Visit	1	2[a]	3[a]	4[a]	5[b]	6[b]	7[a]	8[a]	9[b]	10[b]	11[b]	12[b]	13[b]	14[b]	15[b]	16[b]	17[b]	18	19[c]
Study Week	**-4 to -2**	**-1**	**0**	**2**	**6**	**10**	**12**	**14**	**18**	**22**	**26**	**30**	**34**	**38**	**42**	**46**	**52**	**53**	**54**
Informed consent	X																		
Medical history	X																		
Diagnosis/RLS-SFDQ-9/RLS-HCDI	X																		
Physical examination	X						X				X						X		
Electrocardiogram	X		X				X				X						X		
Vital sign (supine and standing)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Body weight	X						X				X						X		
Hematology	X						X				X						X		
Chemistry	X						X				X						X		
Serum ferritin	X						X				X						X		
Urinalysis[d]	X						X				X						X		
Pregnancy test[e,f]	X		X				X				X						X		
Urine drug screen[f]	X		X				X				X						X		
Eligibility assessment	X	X	X																
Randomization			X																
IRLS		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
VAS-limb pain			X	X	X	X	X												
CGI-S	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
CGI-I				X	X	X	X	X	X	X	X	X	X	X	X	X	X		
C-SSRS	X[g]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	
Barratt scale			X				X				X						X		
MOS-SS, RLS-QoL, SF-36 SIDA-RLS, ASRS, life-style narrative[i]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
POMS			X	X	X	X	X												
Diary[j], SSQ[k], RLS-NDI[l] (dispense/collect)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
WPAI-SHP			X				X										X		
Drug dispensing		X[m]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[n]		
Concomitant medication record	X----------X																		
Adverse event		X----------X																	

Table 1. Schedule of Activities

ASRS = Augmentation Severity Rating Scale; CGI-I = Clinical Global Impression–Improvement; CGI-S = Clinical Global Impressions–Severity; C-SSRS = Columbia–Suicide Severity Rating Scale; IRB = Institutional Review Board; IEC = Independent Ethics Committee; IRLS = International Restless Leg Group Rating Scale; MOS-SS = Medical Outcomes Study-Sleep Scale; POMS = Profile of Mood State; RLS-HCDI = Restless Legs Syndrome-Hening Clinical Diagnostic Interview; RLS-SFDQ-9 = Restless Legs Syndrome - Short Form Diagnostic Questionnaire; RLS-QoL = Restless Leg Syndrome - Quality of Life; RLS-NDI = RLS-Next-day impact; SF-36 = Short Form 36; SIDA-RLS = Structured Interview for Diagnosis of Augmentation-RLS; SSQ = Subjective Sleep Questionnaire; VAS-limb pain = limb pain rating using a visual analog scale; WPAI-SHP = Work Productivity and Activity Impairment Questionnaire-Specific Health Problem.

a. The allowed visit window was ±3 days, except for Visit 3. The window for Visit 3 was +3 days. However, in the event the study medication was not available at the time of randomization, an additional placebo run-in pack may have been dispensed at Visit 3, therefore, extending the visit 3 window to +7 days.
b. The allowed visit window was ±7 days.
c. Optional at the discretion of Investigator's regarding unresolved queries.
d. Dipstick test was to be performed at study site. Samples were to be sent to central laboratory for microscopy only if urine dipstick was positive for blood or protein.
e. Women of child-bearing-potential only. A urine pregnancy test was preferred for this study; however, plasma serum pregnancy test may have been conducted if required by local regulation. Tests were repeated per a request of IRB/IECs, or if required by local regulators.
f. Performed at study site using a dipstick. The sample was then submitted to central laboratory for confirmation.
g. C-SSRS (Baseline).
h. C-SSRS (since last visit).
i. Completed by Investigator only when augmentation trigger criteria were met.
j. Completed by subjects twice a day for 7 consecutive days prior to clinical visit; subjects returned the diary at the clinical visit.
k. Completed by subjects at home every morning within 30 minutes of waking-up for 7 consecutive days prior to clinical visit; subjects returned the diary at the clinical visit.
l. Completed by subjects at home at the end of the day before going to bed for 7 consecutive days prior to clinical visit; subjects returned the diary at the clinical visit.
m. Single-blind, placebo run-in.
n. Taper pack.

Number of Subjects (Planned and Analyzed): A total of 1379 subjects were planned and enrolled, and 731 were assigned to a study treatment. Of those assigned to study treatment, 719 subjects received at least 1 dose. There were 354 subjects who completed the study, and 365 subjects discontinued.

Diagnosis and Main Criteria for Inclusion: Men or women at least 18 years of age, inclusive, with idiopathic RLS in the presence of all 4 RLS clinical manifestations, and having symptoms predominantly occurring in the evening were eligible to participate in the study. Subjects had a history of RLS symptoms for at least 6 months and have an International Restless Leg Group Rating Scale (IRLS) total score ≥15 at beginning of placebo run-in (1 week before Baseline) and end of placebo run-in (at Baseline). Subjects had RLS symptoms ≥15 nights during the month prior to Screening. Subjects receiving RLS therapy at Screening had RLS symptoms ≥15 nights per month prior to initiation of study treatment, and had RLS symptoms ≥2 nights during the week of placebo run-in. Subjects with any secondary RLS were excluded or with RLS treatment augmentation at Screening.

Study Treatment: Doses for active treatments were escalated to the assigned fixed dose during the first 2 weeks of treatment. Subjects assigned to placebo received a matching placebo escalation scheme. After Week 12, placebo subjects were redistributed to 1 of the 3 active treatments and the dose was escalated in an identical manner to the assigned fixed dose over 2 weeks as described in Table 2. Subjects continuing on active treatment received their active dose plus matching placebo capsules in a blinded fashion over this 2-week period. At the end of the study (12 months), all the subjects, including those who discontinued from the study after being treated with study medication for at least 2 weeks or longer but before the 12-month time point, were to be tapered off their study medication over 1 week as described in Table 3.

Table 2. Pregabalin and Pramipexole Dose-Escalation Schedule

Target Dose	Day 1-5 (mg/Day)	Day 6-10 (mg/Day)	Day 11 Onward (mg/Day)
Pregabalin 300 mg/day	75	150	300
Pramipexole 0.5 mg/day	0.125	0.25	0.50
Pramipexole 0.25 mg/day	0.125	0.25	0.25

Table 3. Pregabalin and Pramipexole Dose-Tapering Schedule

Target Dose	Day 1-3 (mg/Day)	Day 4-6 (mg/Day)	Day 7 (mg/Day)
Pregabalin 300 mg/day	150	75	Placebo
Pramipexole 0.5 mg/day	0.25	0.125	Placebo
Pramipexole 0.25 mg/day	0.125	Placebo	Placebo

Efficacy and Safety Endpoints:

Primary:

- Changes from Baseline in RLS symptom severity using the IRLS total score for efficacy assessment;
- The proportion of subjects responding to treatment using the Clinical Global Impression–Improvement (CGI-I) scale for efficacy assessment. Responders were defined as those who report CGI-I scores of "very much improved" or "much improved";
- Rate of augmentation over 9 or 12 months was determined by the centralized Adjudication Board by reviewing all cases that passed a set of assessment for potential augmentation. The assessment will rely upon a set of criteria including:
  - The Structured Interview for Diagnosis of Augmentation during RLS treatment (SIDA-RLS) based on augmentation diagnostic criteria established by Allen et al, in 2003; or
  - Augmentation Severity Scale (ASRS); or
  - Clinical judgment that augmentation might be present.

Secondary:

- Subjective Sleep Questionnaire (SSQ)-Subjective Wake after sleep onset (WASO);
- RLS-Next Day Impact (RLS-NDI);
- Limb pain rating using a visual analog scale (Limb Pain-VAS);
- Severity of augmentation symptoms using ASRS total score;
- Subjective Sleep Questionnaire (SSQ);
- Clinical Global Impressions–Severity (CGI-S);
- Medical Outcomes Study-Sleep Scale (MOS - SS);
- Profile of Mood State (POMS);
- RLS-Quality of Life (RLS-QoL) Scale;
- Medical Outcomes Study-Short Form 36 (SF-36);

- Work Productivity and Activity Impairment Questionnaire-Specific Health Problem (WPAI-SHP).

Safety:

- Adverse events (AEs) from spontaneous reports were monitored throughout the trial and summarized by treatment group;
- The laboratory findings data were summarized by treatment group;
- Columbia–Suicide Severity Rating Scale (C-SSRS) was utilized to assess the risk of suicide;
- Barratt Impulsiveness Scale (Barratt Scale) was collected to assess the risks of impulsive behavior;
- Changes in RLS symptoms following the discontinuation of study drug at the end of treatment was evaluated by collection of the IRLS scores at the end of the drug taper period at Week 53.

Safety Evaluations: Safety evaluations included AE monitoring, laboratory tests, electrocardiograms (ECGs), physical examinations, vital signs (blood pressure and pulse), and body weight. Suicidal behavior was assessed using the Columbia–Suicide Severity Rating Scale (C-SSRS).

Statistical Methods: The population analysis sets included:

- Full Analysis Set (FAS): Primary and secondary analyses were conducted for the intent-to-treat (ITT) population, which is defined as the set of randomized subjects who took at least 1 dose of randomized study medication and had at least 1 postrandomization efficacy assessment on any efficacy scale.
- Evaluable Analysis Sets: Sensitivity analyses for augmentation and long term comparable efficacy analysis was conducted on the evaluable dataset according to which treatment subjects actually received, regardless of their randomized drug assignment. Subjects with major protocol violations were not included in this analysis set.
- Safety Analysis Set: The safety analysis dataset is defined as those subjects who received at least 1 dose of active treatment.

All efficacy analyses were conducted for the ITT population.

Standard descriptive analyses of the safety data included summaries of AEs, discontinuation rates, concomitant medications, and vital sign by treatment group. The C-SSRS was summarized by treatment over the course of the study.

RESULTS

Subject Disposition and Demography: A total of 1379 subjects were screened, and 731 were assigned to a study treatment. Of those assigned to study treatment, 719 subjects received at least 1 dose. There were 354 (48.4%) subjects who completed the study, and 365 (49.9%) subjects discontinued. There were 127 (17.7%) subjects who withdrew due to AEs related to study drug, and 39 (5.4%) subjects who withdrew due to AEs not related to study drug. In addition, there were 198 (27.5%) subjects who discontinued the study for which the relationship to study drug was not defined; these are detailed in Table 4.

Table 4. Subject Disposition

	Pregabalin 300 mg	Pramipexole 0.25 mg	Pramipexole 0.50 mg	Placebo to Pregabalin 300 mg	Placebo to Pramipexole 0.25 mg	Placebo to Pramipexole 0.50 mg	Total
	Number (%) of Subjects						
Screened 1379							
Assigned to study treatment 731							
Treated	182	178	180	59	59	61	719
Completed	93 (51.1)	82 (46.1)	89 (49.4)	32 (54.2)	29 (49.2)	29 (47.5)	354 (48.4)
Discontinued overall	89 (48.9)	96 (53.9)	91 (50.6)	27 (45.8)	30 (50.8)	32 (52.5)	365 (49.9)
Discontinued period 1 (first 12 weeks)	55 (30.2)	60 (33.7)	54 (30.0)	14 (23.7)	19 (32.2)	18 (29.5)	220 (30.1)
Discontinuations overall							
Death	0	0	0	1 (1.7)	0	0	1 (0.1)
Relation to study drug not defined	37 (20.3)	61 (34.3)	47 (26.1)	9 (15.3)	21 (35.6)	23 (37.7)	198 (27.5)
Does not meet entrance criteria	3 (1.6)	1 (0.6)	2 (1.1)	0	0	0	6 (0.8)
Insufficient clinical response	5 (2.7)	18 (10.1)	13 (7.2)	4 (6.8)	8 (13.6)	7 (11.5)	55 (7.6)
Lost to follow-up	8 (4.4)	14. (7.9)	8 (4.4)	2 (3.4)	6 (10.2)	6 (9.8)	44 (6.1)
No longer willing to participate in study	14 (7.7)	15 (8.4)	8 (4.4)	2 (3.4)	5 (8.5)	3 (4.9)	47 (6.5)
Other	1 (0.5)	5 (2.8)	7 (3.9)	1 (1.7)	0	4 (6.6)	18 (2.5)
Protocol violation	6 (3.3)	8 (4.5)	9 (5.0)	0	2 (3.4)	3 (4.9)	28 (3.9)
Related to study drug	44 (24.2)	26 (14.6)	31 (17.2)	13 (22.0)	6 (10.2)	7 (11.5)	127 (17.7)
Adverse event	44 (24.2)	26 (14.6)	31 (17.2)	13 (22.0)	6 (10.2)	7 (11.5)	127 (17.7)
Not related to study drug	8 (4.4)	9 (5.1)	13 (7.2)	4 (6.8)	3 (5.1)	2 (3.3)	39 (5.4)
Adverse event	8 (4.4)	9 (5.1)	13 (7.2)	4 (6.8)	3 (5.1)	2 (3.3)	39 (5.4)

Discontinuations occurring outside the lag period were attributed to the last study treatment received.

Data Sets Analyzed: A total of 731 subjects were assigned to receive study treatment, and 719 subjects were dosed. Of these, 698 (95.5%) subjects were included in the ITT population. All subjects who were treated with study drug were analyzed for AEs, and 661 (90.4%) subjects were analyzed for laboratory data. A summary of data sets analyzed is provided in Table 5.

Table 5. Data Sets Analyzed

		Pregabalin 300 mg	Pramipexole 0.25 mg	Pramipexole 0.50 mg	Placebo to Pregabalin 300 mg	Placebo to Pramipexole 0.25 mg	Placebo to Pramipexole 0.50 mg	Total
		Number (%) of Subjects						
Assigned to study treatment	731							
Treated		182	178	180	59	59	61	719
Analyzed for safety								
Adverse events		182 (100)	178 (100)	180 (100)	59 (100)	59 (100)	61 (100)	719 (98.4)
Laboratory data		168 (92.3)	160 (89.9)	169 (93.9)	57 (96.6)	54 (91.5)	53 (86.9)	661 (90.4)
Analyzed for efficacy								
Intent-to-treat[a]		177 (97.3)	169 (94.9)	178 (98.9)	59 (100)	58 (98.3)	57 (93.4)	698 (95.5)

a. Subjects who were treated and had at least 1 baseline and postbaseline efficacy measurements were included.

Demographic and Other Baseline Characteristics: The age of the subjects ranged from 19 to 82 years. The subjects were predominantly White, and there were no major differences between treatment groups in terms of race breakdown. All groups had more females than males, with the difference being most notable in the pregabalin 300 mg group. There were no meaningful differences in mean weight, height, or body mass index between groups; the weight of the subjects across all groups ranged from 43.6 kg to 172.7 kg.

Table 6. Demographic Characteristics

	Pregabalin 300 mg N=182	Pramipexole 0.25 mg N=178	Pramipexole 0.50 mg N=180	Placebo to Pregabalin 300 mg N=59	Placebo to Pramipexole 0.25 mg N=59	Placebo to Pramipexole 0.50 mg N=61
Gender						
Male	59	70	81	22	23	23
Female	123	108	99	37	36	38
Age (years):						
Mean (SD)	54.3 (13.0)	56.5 (12.8)	54.2 (13.5)	57.0 (13.3)	51.9 (13.6)	51.5 (12.6)
Range	20-79	25-82	24-80	24-76	19-73	28-79
Race, n (%):						
White	150 (82.4)	152 (85.4)	151 (83.9)	52 (88.1)	48 (81.4)	52 (85.2)
Black	7 (3.8)	10 (5.6)	10 (5.6)	2 (3.4)	1 (1.7)	2 (3.3)
Asian	2 (1.1)	2 (1.1)	2 (1.1)	0	0	0
Other	9 (4.9)	4 (2.2)	3 (1.7)	2 (3.4)	3 (5.1)	1 (1.6)
Unspecified	14 (7.7)	10 (5.6)	14 (7.8)	3 (5.1)	7 (11.9)	6 (9.8)
Weight (kg):						
Mean (SD)	79.4 (16.1)	82.1 (16.8)	81.3 (17.9)	81.8 (17.9)	82.0 (16.3)	81.9 (16.8)
Range	50.0-164.0	52.0-145.6	51.0-172.7	48.0-130.0	43.6-123.0	56.0-131.2
Body mass index (kg/m^2):						
Mean (SD)	28.0 (5.0)	28.6 (5.2)	28.2 (5.2)	28.9 (5.9)	28.2 (5.0)	28.1 (5.2)
Range	18.8-49.5	19.5-43.5	18.8-49.6	18.5-42.9	20.2-43.3	20.6-49.2
Height (cm):						
Mean (SD)	168.3 (9.5)	169.5 (9.8)	169.5 (10.2)	168.2 (9.2)	170.4 (9.3)	170.7 (9.9)
Range	145.0-204.0	142.0-196.0	145.0-193.0	148.0-185.4	145.0-188.0	152.4-194.0

Body mass index was calculated as weight/(height × 0.01)^2.
N = number of subjects; n = number of subjects in specified category; SD = standard deviation.

Efficacy Results:

Primary Efficacy Endpoints:

IRLS Total Score 12-Week Assessment for Pregabalin Versus Placebo: Treatment with pregabalin resulted in a statistically significant improvement in RLS symptoms, measured as least square (LS) mean change from Baseline in IRLS total score, averaged across the first 12 weeks of treatment, compared to treatment with placebo ($p<0.0001$) (Table 7). Pramipexole treatment was significant at the 0.5 mg level, but not at the 0.25 mg level, compared with placebo ($p<0.0001$ and $p=0.3603$, respectively).

Table 7. IRLS Total Score: Raw Value and Change From Baseline, Averaging Across First 12 Weeks (Observed Cases) – ITT Population

Visit		Pregabalin 300 mg N=177	Pramipexole 0.25 mg N=169	Pramipexole 0.50 mg N=178	Placebo N=174
Week 0 (Baseline)					
Raw value	n	177	169	178	172
	Min-max	15-39	7-35	15-38	15-39
	Median	21.0	22.0	21.0	21.0
	Mean (SD)	22.3 (5.73)	22.4 (5.37)	22.1 (5.19)	22.4 (5.58)
	95% CI of mean	21.5, 23.2	21.6, 23.2	21.4, 22.9	21.6, 23.2
First 12 Weeks (Average)					
Change from Baseline	n	177	169	178	172
	95% CI of mean	-12.6, -10.3	-8.8, -6.8	-11.2, -9.1	-7.9, -6.0
	SD	7.78	6.77	7.16	6.34
	LS mean	-11.8	-7.9	-10.5	-7.3
	95% CI of LS mean	-12.7, -10.9	-8.8, -6.9	-11.4, -9.5	-8.2, -6.3
	SE	0.47	0.49	0.47	0.48
	Versus placebo				
	LS mean difference	-4.5	-0.6	-3.2	
	95% CI of LS mean difference	-5.9, -3.2	-2.0, 0.7	-4.5, -1.9	
	SE	0.67	0.68	0.67	
	p-Value	<0.0001	0.3603	<0.0001	

Total scores range from 0 to 40. Lower score indicates lower severity and better quality of life. Estimates and p-values were from a mixed model and spatial power covariance structure including fixed effects for baseline value, region, treatment, and week.
CI = confidence interval; IRLS = International Restless Leg Group Rating Scale; ITT = intent-to-treat; LS mean = least square mean; N = number of subjects; SD = standard deviation; SE = standard error.

Subscales of IRLS focusing on symptom severity and impact on daily living were also analyzed. Consistent with the earlier displayed IRLS total score data, the pregabalin 300 mg and the pramipexole 0.50 mg treatment groups demonstrated statistically significant differences in LS mean changes from Baseline compared with placebo in IRLS symptom severity scores, averaged across the first 12 weeks, while pramipexole 0.25 mg treatment did not (Table 8).

Table 8. IRLS Symptom Severity Score: Averaging Across First 12 Weeks (Observed Cases) – ITT Population

Visit		Pregabalin 300 mg N=177	Pramipexole 0.25 mg N=169	Pramipexole 0.50 mg N=178	Placebo N=174
Week 0 (Baseline)					
Raw value	n	177	169	178	172
	Min-max	9-24	6-24	9-24	10-24
	Medium	15.0	16.0	15.0	16.0
	Mean (SD)	16.2 (3.49)	16.2 (3.52)	16.1 (3.41)	16.2 (3.43)
	95% CI of mean	15.7, 16.7	15.7, 16.7	15.6, 16.6	15.6, 16.7
First 12 Weeks (Average)					
Change from Baseline	n	177	169	178	172
	95% CI of mean	-8.9, -7.3	-6.2, -4.7	-8.0, -6.4	-5.4, -4.1
	SD	-5.32	4.74	5.32	4.32
	LS mean	-8.4	-5.5	-7.4	-5.0
	95% CI of LS mean	-9.0, -7.7	-6.2, -4.9	-8.1, -6.8	-5.6, -4.3
	SE	0.34	0.35	0.33	0.34
	Versus placebo				
	LS mean difference	-3.4	-0.6	-2.5	
	95% CI of LS mean difference	-4.3, -2.5	-1.5, 0.4	-3.4, -1.5	
	SE	0.48	0.48	0.48	
	p-Value	<0.0001	0.2443	<0.0001	

Subscale of symptom severity = Sum of items (1, 2, 4, 6, 7, 8). It ranges from 0 to 14. Lower score indicates lower symptom severity. Estimates and p-values were from a mixed model and spatial-power covariance structure including fixed effects for baseline value, region, treatment, and week.
CI = confidence interval; IRLS = International Restless Leg Group Rating Scale; ITT = intent-to-treat; LS mean = least square mean; N = number of subjects; SD = standard deviation; SE = standard error.

Clinical Global Impression–Improvement (CGI-I) Responders 12-Week Assessment for Pregabalin Versus Placebo: For the CGI-I assessment, there was a significantly greater percentage of responders in the pregabalin 300 mg and pramipexole 0.50 mg treatment groups (Table 9) compared to the placebo group for all measured time points (Weeks 2, 6, 10, 12, and Week 12 last observation carried forward [LOCF]); in the pramipexole 0.25 mg treatment group.

Table 9. Clinical Global Impressions Improvement Responders at Week 12 (LOCF), Overall and By Region – ITT Population

Visit	CGI-I Responder Status	Pregabalin 300 mg N=177 n (%)	Pramipexole 0.25 mg N=169 n (%)	Pramipexole 0.50 mg N=178 n (%)	Placebo N=174 n (%)
Week 12 (LOCF)					
	n	175	168	177	173
	Responders	125 (71.4)	86 (51.2)	111 (62.7)	81 (46.8)
	Nonresponders	50 (28.6)	82 (48.8)	66 (37.3)	92 (53.2)
	Versus placebo				
	Pairwise p-value	<0.0001	0.4393	0.0022	
Week 12 (LOCF)					
EU	n	110	103	108	96
	Responders	85 (77.3)	56 (54.4)	62 (57.4)	44 (45.8)
	Nonresponders	25 (22.7)	47 (45.6)	46 (42.6)	52 (54.2)
	Versus placebo				
	Pairwise p-value	<0.0001	0.2300	0.0995	
Week 12 (LOCF)					
US	n	65	65	69	77
	Responders	40 (61.5)	30 (46.2)	49 (71.0)	37 (48.1)
	Nonresponders	25 (38.5)	35 (53.8)	20 (29.0)	40 (51.9)
	Versus placebo				
	Pairwise p-value	0.1093	0.8220	0.0050	

Analysis used Cochran-Mantel-Haenszel method. Responders were defined as subjects who reported CGI-I scores of very much improved or much improved for a given visit. Nonresponders were defined as subjects who did not report CGI-I scores of very much improved or much improved for a given visit.
CGI-I = Clinical Global Impressions – Improvement; ITT = intent-to-treat; LOCF = last observation carried forward; N = number of subjects; n = number of subjects in the specified category; EU = European Union; US = United States.

Augmentation Rates 52-Week Assessment: There was a significantly lower number and percentage of subjects with augmentation in the pregabalin 300 mg treatment group compared with the pramipexole 0.50 mg treatment group. The number and percentage of augmentation was numerically lower in the pregabalin 300 mg group compared with the pramipexole 0.25 mg group; however, the difference did not reach statistical significance Table 10.

Table 10. Augmentation Rate Analysis, Pregabalin Versus Pramipexole Using Stratified Log-Rank Test by Block – ITT Population

Treatment Group		Block 40[a]	Block 52[b]	Pregabalin vs Pramipexole p-Value[c]
Pregabalin 300 mg	N	59	176	
	Subjects censored (%)	57 (96.6)	173 (98.3)	
	Subjects having augmentation (%)	2 (3.4)	3 (1.7)	
Pramipexole 0.25 mg	N	58	167	0.0826
	Subjects censored (%)	57 (98.3)	156 (93.4)	
	Subjects having augmentation (%)	1 (1.7)	11 (6.6)	
Pramipexole 0.5 mg	N	57	178	0.0012
	Subjects censored (%)	55 (96.5)	162 (91.0)	
	Subjects having augmentation (%)	2 (3.5)	16 (9.0)	

ITT = intent-to-treat; N = number of subjects; vs = versus.
a. Placebo turned active subjects had a potential of getting 40 weeks of active treatment after 12 weeks on placebo.
b. All on active subjects had a potential of getting 52 weeks of active treatment during the entire study.
c. p-value was obtained using Stratified log-rank test by block.

Secondary Efficacy Endpoints:

Comparability of Efficacy of Pregabalin and Pramipexole: Noninferiority assessment was performed for the change from Baseline in IRLS total score in the short-term (for the first 12 weeks) and the long-term (for 52 weeks), using both fixed-margin (Table 11) and random-margin approaches. All comparisons had an upper bound of the 1-sided 97.5% CI below the specified noninferiority margin and were statistically significant, except for the short-term pramipexole 0.25 mg versus pramipexole 0.50 mg in the ITT population.

Table 11. IRLS Total Score Change From Baseline, Noninferiority Assessment– Pregabalin Versus Pramipexole – ITT Population

	N1/N2	LS Mean Difference	One-Sided p-Value	97.5% CI Upper Bound
Analysis using 3-point fixed margin				
Short-term (12 weeks):				
Pregabalin 300 mg vs. pramipexole 0.25 mg	177/169	-3.964	<0.0001	-2.809
Pregabalin 300 mg vs. pramipexole 0.50 mg	177/178	-1.686	<0.0001	-0.548
Long-term (52 weeks):				
Pregabalin 300 mg vs. pramipexole 0.25 mg	129/121	-3.799	<0.0001	-2.711
Pregabalin 300 mg vs. pramipexole 0.50 mg	129/133	-3.062	<0.0001	-1.990

CI = confidence interval; IRLS = International Restless Leg Group Rating Scale; ITT = intent-to-treat; LS mean = least square mean; N = number of subjects.

Subjective Sleep Questionnaire-Wake After Sleep Onset (SSQ-WASO) Over 12 Weeks: The results of the SSQ–WASO, averaged across the first 12 weeks for the ITT population, were not formally tested for statistical significance, as the gatekeeping procedure used to protect the Type I error was stopped prior to evaluating this endpoint. However, the results of the SSQ-WASO analyses demonstrated a nominally greater decrease (pregabalin 300 mg: LS mean difference = -17.25, p<0.0001) with pregabalin compared with placebo, but not for either pramipexole treatment group (Table 12).

Table 12. Subjective Sleep Questionnaire–Total Wake After Sleep Onset (WASO): Averaging Across First 12 Weeks (Observed Cases) – ITT Population

Visit		Pregabalin 300 mg N=177	Pramipexole 0.25 mg N=169	Pramipexole 0.50 mg N=178	Placebo N=174
Week 0 (Baseline)					
Raw value (minutes)	n	168	158	169	163
	Min-max	0-351	0-437	0-339	0-334
	Median	79.0	80.0	60.0	59.2
	Mean (SD)	90.6 (76.10)	100.2 (85.92)	83.9 (77.35)	79.5 (69.85)
	95% CI of mean	79.0, 102.2	86.7, 113.7	72.2, 95.7	68.6, 90.3
First 12 Weeks (Average)					
Change from Baseline (minutes)	n	167	158	168	163
	95% CI of mean	-56.6, -39.1	-48.4, -26.4	-42.9, -22.7	-34.6, -19.7
	SD	57.13	70.09	66.27	48.24
	LS mean	-49.86	-33.69	-37.18	-32.61
	95% CI of LS mean	-55.87, -43.86	-39.87, -27.51	-43.15, -31.21	-38.70, -26.53
	SE	3.057	3.146	3.039	3.100
	Versus placebo				
	LS mean difference	-17.25	-1.07	-4.57	
	95% CI of LS mean difference	-25.76, -8.74	-9.73, 7.58	-13.05, 3.91	
	SE	4.332	4.408	4.318	
	p-Value	<0.0001	0.8075	0.2906	

Subscale of total wake up time after sleep onset ranges from 0 to 1440 minutes. Lower values indicate better sleep.
Estimates and p-values were from a mixed model and spatial power covariance structure including fixed effects for baseline value, region, treatment, and week.
CI = confidence interval; ITT = intent-to-treat; LS mean = least square mean; Max = maximum; Min = minimum; N = number of subjects; n = number of subjects in the specified category; SD = standard deviation; SE = standard error.

Restless Leg Syndrome-Next-Day Impact (RLS-NDI) Over 12 Weeks: The results from RLS-NDI total score, averaged across the first 12 weeks, were not formally tested for statistical significance as the gatekeeping procedure was stopped prior to evaluating this endpoint. However, RLS-NDI total score demonstrated a nominal decrease in LS mean difference with pramipexole 0.50 mg treatment compared with placebo, but not with pregabalin 300 mg treatment, and that there was an increase with pramipexole 0.25 mg treatment compared with placebo (Table 13).

Table 13. RLS-NDI Total Score: Averaging Across First 12 Weeks (Observed Cases)– ITT Population

Visit		Pregabalin 300 mg N=177	Pramipexole 0.25 mg N=169	Pramipexole 0.50 mg N=178	Placebo N=174
Week 0 (Baseline)					
Raw value	n	26	30	34	31
	Min-max	3-94	19-105	22-115	8-89
	Median	54.5	48.0	58.1	47.9
	Mean (SD)	49.3 (22.03)	51.9 (18.62)	58.4 (20.27)	50.0 (22.64)
	95% CI of mean	40.4, 58.2	45.0, 58.9	51.3, 65.5	41.7, 58.3
First 12 Weeks (Average)					
Change from Baseline	n	26	30	34	31
	95% CI of mean	-9.5, -1.2	-7.5, 1.6	-15.7, -6.2	-9.0, 0.3
	SD	10.25	12.26	13.65	12.58
	LS mean	-8.1	-4.3	-14.5	-6.6
	95% CI of LS mean	-13.8, -2.4	-9.5, 1.0	-19.5, -9.6	-12.0, -1.3
	SE	2.88	2.65	2.50	2.68
	Versus placebo				
	LS mean difference	-1.5	2.4	-7.9	
	95% CI of LS mean difference	-9.3, 6.3	-5.1, 9.9	-15.2, -0.5	
	SE	3.93	3.78	3.69	
	p-Value	0.7073	0.5299	0.0354	

Estimates and p-values were from a mixed model and spatial power covariance structure including fixed effects for baseline value, region, treatment, and week.
CI = confidence interval; ITT = intent-to-treat; Max = maximum; Min = minimum; N = number of subjects; n = number of subjects in the specified category; RLS-NDI = restless leg syndrome – next-day impact; SD = standard deviation; LS mean = least square mean; SE = standard error.

Limb Pain Rating Using a Visual Analog Scale Over 12 Weeks: The results from the limb pain VAS, averaged across the first 12 weeks for the ITT population, were not formally tested for statistical significance, as the gatekeeping procedure was stopped prior to evaluating this endpoint. However, limb pain VAS demonstrated a greater decrease in LS mean difference compared to placebo for the pregabalin 300 mg treatment group (LS mean difference = -1, p=0.0004), but not for the pramipexole treatment groups (Table 14).

Table 14. Visual Analog Scale–Limb Pain: Averaging Across First 12 Weeks (Observed Cases) – ITT Population

Visit		Pregabalin 300 mg N=177	Pramipexole 0.25 mg N=169	Pramipexole 0.50 mg N=178	Placebo N=174
Week 0 (Baseline)					
Raw value	n	163	155	167	158
	Min-max	0-10	0-10	0-9	0-10
	Median	4.5	4.6	3.8	4.5
	Mean (SD)	4.2 (2.70)	4.3 (2.58)	4.0 (2.53)	4.1 (2.52)
	95% CI of mean	3.7, 4.6	3.9, 4.7	3.6, 4.4	3.7, 4.5
First 12 Weeks (Average)					
Change from Baseline	n	163	155	167	158
	95% CI of mean	-2.3, -1.5	-1.6, -0.8	-1.5, -0.7	-1.2, -0.5
	SD	2.78	2.56	2.67	2.27
	LS mean	-3.20	-2.64	-2.75	-2.20
	95% CI of LS mean	-3.60. -2.81	-3.04, -2.24	-3.17, -2.34	-2.59, -1.81
	SE	0.201	0.204	0.210	0.198
	Versus placebo				
	LS mean difference	-1.00	-0.43	-0.55	
	95% CI of LS mean difference	-1.55, -0.45	-0.99, 0.12	-1.12, 0.01	
	SE	0.280	0.282	0.287	
	p-Value	0.0004	0.1242	0.0553	

Limb pain score ranges from 0 to 100 and lower score indicates lower limb pain. Estimates and p-values were from a mixed model and spatial power covariance structure including fixed effects for baseline value, region, treatment, and week.
CI = confidence interval; ITT = intent-to-treat; LS mean = least square mean; Max = maximum; Min = minimum; N = number of subjects; n = number of subjects in the specified category; SD = standard deviation; SE = standard error.

Severity of Augmentation Symptoms Using Augmentation Severity Rating Scale (ASRS) Total Score: The results from the ASRS total score (Table 15), averaged across the long-term (52 weeks) period for the ITT population, were not included in the gatekeeping procedure used to protect the Type I error. However, ASRS total score demonstrated less severe augmentation in the pregabalin 300 mg treatment group compared to pramipexole 0.25 mg and 0.5 mg (LS mean difference = -0.83, $p<0.0001$; LS mean difference = -0.76, $p<0.0001$, respectively). Similar results were observed for the short-term (12 weeks) period.

Table 15. ASRS Total Score: Short-Term and Long-Term Assessment – ITT Population

Average Across Weeks	N1/N2	LS Mean 1 /LS Mean 2	LS Mean Difference	95% CI	p-Value
Short-term					
PGB 300 mg vs. PPX 0.25 mg	176/167	0.797/1.680	-0.883	-1.239, -0.528	<0.0001
PGB 300 mg vs PPX 0.50 mg	176/177	0.797/1.174	-0.377	-0.728, -0.026	0.0354
PPX 0.25 mg vs. PPX 0.50 mg	167/177	1.680/1.174	0.507	0.150, 0.863	0.0054
Long-term					
PGB 300 mg vs PPX 0.25 mg	127/117	0.748/1.578	-0.830	-1.136, -0.523	<0.0001
PGB 300 mg vs PPX 0.50 mg	127/128	0.748/1.508	-0.760	-1.062, -0.457	<0.0001
PPX 0.25 mg vs PPX 0.50 mg	117/128	1.578/1.508	0.070	-0.239, 0.379	0.6570

Estimates and p-values are from a mixed model including fixed effects for region, treatment, period (before or after Week 12), week, treatment-by-period, and treatment-by-week interaction.
Short-term = 12 weeks; long-term = 52 weeks. Higher scores indicate more severe augmentation.
ASRS = Augmentation Severity Rating Scale; CI = confidence interval; ITT = intent to treat; LS = least square; N = number of subjects; PGB = pregabalin; PPX = pramipexole; vs = versus.

Subjective Sleep Questionnaire:Other Subscales: The results of SSQ subscales averaged across the first 12 weeks for the ITT population were not included in the gatekeeping procedure used to protect the Type I error.

Sleep Latency: The results from the SSQ latency analysis, averaged across the first 12 weeks for the ITT population, demonstrated greater decrease in LS mean difference compared to placebo for both of the pramipexole treatment groups, but not for the pregabalin 300 mg treatment group (Table 16).

Table 16. Subjective Sleep Questionnaire-Latency: Averaging Across First 12 Weeks (Observed Cases) – ITT Population

Visit		Pregabalin 300 mg N=177	Pramipexole 0.25 mg N=169	Pramipexole 0.50 mg N=178	Placebo N=174
Week 0 (Baseline)					
Raw value	n	170	161	174	165
	Min-max	4-291	3-400	3-330	4-283
	Median	46.1	55.0	45.4	47.1
	Mean (SD)	55.9 (42.18)	67.8 (56.83)	61.5 (55.11)	58.7 (49.91)
	95% CI of mean	49.5, 62.2	58.9, 76.6	53.3, 69.7	51.0, 66.4
First 12 Weeks (Average)					
Change from Baseline	n	169	161	174	165
	95% CI of mean	-19.4, -9.4	-31.9, -17.4	-33.8, -17.3	-16.2, -5.8
	SD	33.04	46.42	55.19	33.87
	LS mean	-17.99	-20.75	-25.57	-12.51
	95% CI of LS mean	-22.20, -13.77	-25.08. -16.42	-29.70, -21.44	-16.76, -8.26
	SE	2.147	2.204	2.104	2.164
	Versus placebo				
	LS mean difference	-5.48	-8.24	-13.06	
	95% CI of LS mean difference	-11.44, 0.48	-14.29, -2.19	-18.97, -7.15	
	SE	3.035	3.081	3.011	
	p-Value	0.0715	0.0077	<0.0001	

Subscale of latency ranges from 0 to 840 minutes and lower value indicates better sleep. Estimates and p-values were from a mixed model and spatial power covariance structure including fixed effects for baseline value, region, treatment, and week.
CI = confidence interval; ITT = intent-to-treat; LS mean = least square mean; Max = maximum; Min = minimum; N = number of subjects; n = number of subjects in the specified category; SD = standard deviation; SE = standard error.

Subjective Total Sleep Time: The results of the analysis of subjective total sleep time (sTST), expressed as hours of sleep, averaged across the first 12 weeks for the ITT population, demonstrated greater increase in LS mean difference compared to placebo for the pregabalin 300 mg treatment group (LS mean difference = 0.43, p<0.0001) and for the pramipexole 0.50 mg treatment group (LS mean difference = 0.18, p=0.0272), but not for the pramipexole 0.25 mg treatment group (Table 17).

Table 17. Subjective Sleep Questionnaire-sTST: Averaging Across First 12 Weeks (Observed Cases) – ITT Population

Visit		Pregabalin 300 mg N=177	Pramipexole 0.25 mg N=169	Pramipexole 0.50 mg N=178	Placebo N=174
Week 0 (Baseline)					
Raw value (hours)	n	170	161	174	165
	Min-max	2-9	2-10	2-9	3-10
	Median	6.2	6.4	6.4	6.4
	Mean (SD)	6.1 (1.35)	6.2 (1.36)	6.2 (1.27)	6.3 (1.31)
	95% CI of mean	5.9, 6.3	6.0, 6.4	6.0, 6.4	6.1, 6.5
First 12 Weeks (Average)					
Change from Baseline (hours)	n	170	161	174	165
	95% CI of mean	0.7, 1.0	0.3, 0.7	0.5, 0.8	0.2, 0.5
	SD	1.01	0.99	1.03	0.80
	LS mean	0.87	0.51	0.62	0.43
	95% CI of LS mean	0.75, 0.98	0.40, 0.63	0.50, 0.73	0.32, 0.55
	SE	0.059	0.060	0.058	0.060
	Versus placebo				
	LS mean difference	0.43	0.08	0.18	
	95% CI of LS mean difference	0.27. 0.59	-0.09, 0.25	0.02, 0.35	
	SE	0.083	0.084	0.083	
	p-Value	<0.0001	0.3483	0.0272	

Subscale of hours of sleep ranges from 0 to 16 hours and higher value indicates better sleep (but it should not go well beyond 8 hours). Estimates and p-values were from a mixed model and spatial power covariance structure including fixed effects for baseline value, region, treatment, and week.
CI = confidence interval; ITT = intent-to-treat; LS mean = least square mean; Max = maximum; Min = minimum; N = number of subjects; n = number of subjects in the specified category; SD = standard deviation; SE = standard error.

Subjective Number of Awakenings After Sleep Onset: The results from the SSQ subjective number of awakenings after sleep onset (sNAASO) analysis, averaged across the first 12 weeks for the ITT population, demonstrated a greater decrease in LS mean difference compared to placebo for the pregabalin 300 mg treatment group (LS mean = -0.56, p<0.0001), but not for the pramipexole 0.25 mg or pramipexole 0.50 mg treatment groups (Table 18).

Table 18. Subjective Sleep Questionnaire-sNAASO: Averaging Across First 12 Weeks (Observed Cases) – ITT Population

Visit		Pregabalin 300 mg N=177	Pramipexole 0.25 mg N=169	Pramipexole 0.50 mg N=178	Placebo N=174
Week 0 (Baseline)					
Raw value	n	170	161	174	165
	Min - max	0-10	0-9	0-8	0-24
	Median	2.1	1.9	1.6	2.0
	Mean (SD)	2.3 (1.61)	2.3 (1.45)	1.9 (1.30)	2.4 (2.22)
	95% CI of mean	2.0, 2.5	2.0, 2.5	1.7, 2.1	2.0, 2.7
First 12 Weeks (Average)					
Change from Baseline	n	170	161	174	165
	95% CI of mean	-1.3, -1.0	-0.7, -0.3	-0.6, -0.3	-0.7, -0.4
	SD	1.20	1.18	1.00	0.94
	LS mean	-1.13	-0.52	-0.55	-0.57
	95% CI of LS mean	-1.26, -1.00	-0.66, -0.39	-0.68, -0.42	-0.70, -0.43
	SE	0.067	0.068	0.066	0.067
	Versus placebo				
	LS mean difference	-0.56	0.04	0.02	
	95% CI of LS mean difference	-0.75, -0.38	-0.14, 0.23	-0.17, 0.20	
	SE	0.094	0.096	0.094	
	p-Value	<0.0001	0.6438	0.8456	

Subscale of number of awakenings ranges from 0 to 30, and lower value indicates better sleep. Estimates and p-values were from a mixed model and spatial power covariance structure including fixed effects for baseline value, region, treatment, and week.
CI = confidence interval; ITT = intent-to-treat; LS mean = least square mean; Max = maximum; Min = minimum; N = number of subjects; n = number of subjects in the specified category; sNAASO = subjective number of awakenings after sleep onset; SD = standard deviation; SE = standard error.

Quality of Sleep: The results from the quality of sleep analysis, averaged across the first 12 weeks for the ITT population, demonstrated greater increase compared to placebo for the pregabalin 300 mg treatment group (LS mean = 10.62, p<0.0001), but not for the pramipexole treatment groups (Table 19).

Table 19. Subjective Sleep Questionnaire-Quality of Sleep: Averaging Across First 12 Weeks (Observed Cases) – ITT Population

Visit		Pregabalin 300 mg N = 177	Pramipexole 0.25 mg N = 169	Pramipexole 0.50 mg N = 178	Placebo N = 174
Week 0 (Baseline)					
Raw value	n	169	161	173	165
	Min-max	0-93	4-86	3-100	4-95
	Median	44.2	43.7	45.1	46.3
	Mean (SD)	44.1 (20.62)	44.3 (18.91)	45.5 (20.00)	46.9 (18.15)
	95% CI of mean	41.0, 47.3	41.4, 47.2	42.5, 48.5	44.2, 49.7
First 12 Weeks (Average)					
Change from Baseline	n	169	161	173	165
	95% CI of mean	19.3, 25.6	10.4, 15.8	11.6, 17.9	8.2, 13.4
	SD	20.66	17.33	21.09	17.18
	LS mean	22.65	13.20	15.34	12.02
	95% CI of LS mean	20.15, 25.14	10.64, 15.75	12.90, 17.79	9.51, 14.54
	SE	1.271	1.300	1.247	1.279
	Versus placebo				
	LS mean difference	10.62	1.17	3.32	
	95% CI of LS mean difference	7.10, 14.15	-2.40, 4.74	-0.18, 6.82	
	SE	1.798	1.818	1.781	
	p-Value	<0.0001	0.5191	0.0628	

Subscale of quality of sleep ranges from 0 to 100. Higher score indicates better quality of sleep. Estimates and p-values were from a mixed model and spatial power covariance structure including fixed effects for baseline value, region, treatment, and week.
CI = confidence interval; ITT = intent-to-treat; LS mean = least square mean; Max = maximum; Min = minimum; N = number of subjects; n = number of subjects in the specified category; SD = standard deviation; SE = standard error.

Clinical Global Impressions–Severity: The results from the CGI-S, averaged across the first 12 weeks for the ITT population, demonstrated greater decrease in LS mean difference compared to placebo for the pregabalin 300 mg and for pramipexole 0.50 mg treatment groups but not for the pramipexole 0.25 mg treatment group (Table 20).

Table 20. Clinical Global Impression Severity: Averaging Across First 12 Weeks (Observed Cases) – ITT Population

Visit		Pregabalin 300 mg N=177	Pramipexole 0.25 mg N=169	Pramipexole 0.50 mg N=178	Placebo N=174
Week 0 (Baseline)					
Raw value	n	176	169	178	173
	Min-max	3-7	2-7	3-7	3-7
	Median	5.0	5.0	5.0	5.0
	Mean (SD)	4.7 (0.87)	4.7 (0.95)	4.7 (0.81)	4.7 (0.85)
	95% CI of mean	4.6, 4.9	4.6, 4.8	4.6, 4.8	4.5, 4.8
First 12 Weeks (Average)					
Change from Baseline	n	176	169	178	173
	95% CI of mean	-2.0, -1.6	-1.4, -1.0	-1.8, -1.4	-1.1, -0.8
	SD	1.29	1.19	1.22	1.16
	LS mean	-1.9	-1.3	-1.7	-1.1
	95% CI of LS mean	-2.1, -1.7	-1.4, -1.1	-1.8, -1.5	-1.2, -0.9
	SE	0.08	0.08	0.08	0.08
	Versus placebo				
	LS mean difference	-0.8	-0.2	-0.6	
	95% CI of LS mean difference	-1.0, -0.6	-0.4, 0.0	-0.8, -0.4	
	SE	0.11	0.11	0.11	
	p-Value	<0.0001	0.1237	<0.0001	

Estimates and p-values were from a mixed model and spatial power covariance structure including fixed effects for baseline value, region, treatment, and week.
CI = confidence interval; CGI = clinical global impressions; ITT = intent-to-treat; LS mean = least square mean; Max = maximum; Min = minimum; N = number of subjects; n = number of subjects in the specified category; SD = standard deviation; SE = standard error.

Medical Outcomes Study – Sleep Scale: The MOS-SS results were analyzed by individual subscales. These results, averaged across the first 12 weeks for the ITT population, were not included in the gatekeeping procedures used to protect Type I error.

Pregabalin treatment group demonstrated greater improvement compared to placebo ($p<0.0001$) for the subscales of sleep disturbance (Table 21), adequacy (Table 22), quantity (Table 23), 6 -item sleep index (Table 24), and 9 -item sleep index (Table 25). None of the active treatment groups showed improvement in the subscales of snoring, awakening short of breath, and, somnolence, and optimal sleep.

Table 21. Medical Outcomes Study Sleep Scale-Sleep Disturbance: Averaging Across First 12 Weeks (Observed Cases) – ITT Population

Visit		Pregabalin 300 mg N=177	Pramipexole 0.25 mg N=169	Pramipexole 0.50 mg N=178	Placebo N=174
Week 0 (Baseline)					
Raw value	n	175	169	177	171
	Min-max	5-100	5-100	0-100	0-100
	Median	54.0	54.0	51.0	49.0
	Mean (SD)	53.8 (25.03)	53.1 (24.82)	51.0 (24.55)	50.0 (24.57)
	95% CI of mean	50.1, 57.5	49.3, 56.9	47.3, 54.6	46.3, 53.7
First 12 Weeks (Average)					
Change from Baseline	n	175	169	177	171
	95% CI of mean	-26.6, -20.0	-17.2, -10.4	-19.8, -13.2	-14.4, -8.5
	SD	21.93	22.41	22.17	19.57
	LS mean	-23.3	-14.1	-17.9	-12.4
	95% CI of LS mean	-25.8, -20.8	-16.7, -11.5	-20.4, -15.4	-15.0, -9.9
	SE	1.29	1.32	1.28	1.31
	Versus placebo				
	LS mean difference	-10.9	-1.7	-5.4	
	95% CI of LS mean difference	-14.5, -7.3	-5.3, 2.0	-9.0, -1.9	
	SE	1.84	1.85	1.83	
	p-Value	<0.0001	0.3686	0.0030	

Subscale of sleep disturbance ranges from 0 to 100 with lower score indicating less disturbance. Estimates and p-values were from a mixed model and spatial power covariance structure including fixed effects for baseline value, region, treatment, and week.
CI = confidence interval; ITT = intent-to-treat; LS mean = least square mean; Max = maximum; Min = minimum; N = number of subjects; n = number of subjects in the specified category; SD = standard deviation; SE = standard error.

Table 22. Medical Outcomes Study Sleep Scale-Sleep Adequacy: Averaging Across First 12 Weeks (Observed Cases) – ITT Population

Visit		Pregabalin 300 mg N=177	Pramipexole 0.25 mg N=169	Pramipexole 0.50 mg N=178	Placebo N=174
Week 0 (Baseline)					
Raw value	n	175	168	178	171
	Min-max	0-100	0-90	0-100	0-100
	Median	30.0	30.0	30.0	40.0
	Mean (SD)	34.6 (26.95)	36.8 (26.43)	34.6 (24.89)	37.0 (26.59)
	95% CI of mean	30.6, 38.6	32.8, 40.9	30.9, 38.3	32.9, 41.0
First 12 Weeks (Average)					
Change from Baseline	n	175	168	178	171
	95% CI of mean	16.3, 24.5	9.2, 17.5	11.8, 19.3	6.2, 13.4
	SD	27.37	27.08	25.54	24.09
	LS mean	20.6	14.6	15.3	11.3
	95% CI of LS mean	17.5, 23.6	11.5, 17.7	12.3, 18.4	8.2, 14.4
	SE	1.56	1.60	1.54	1.58
	Versus placebo				
	LS mean difference	9.3	3.3	4.0	
	95% CI of LS mean difference	4.9, 13.6	-1.1, 7.7	-0.3, 8.4	
	SE	2.21	2.24	2.20	
	p-Value	<0.0001	0.1421	0.0680	

Subscale of adequacy ranges from 0 to 100 with higher score indicating greater sleep adequacy.
Estimates and p-values were from a mixed model and spatial power covariance structure including fixed effects for baseline value, region, treatment, and week.
CI = confidence interval; ITT = intent-to-treat; LS mean = least square mean; Max = maximum; Min = minimum;
N = number of subjects; n = number of subjects in the specified category; SD = standard deviation; SE = standard error.

Table 23. Medical Outcomes Study Sleep Scale-Sleep Quantity: Averaging Across First 12 Weeks (Observed Cases) – ITT Population

Visit		Pregabalin 300 mg N=177	Pramipexole 0.25 mg N=169	Pramipexole 0.50 mg N=178	Placebo N=174
Week 0 (Baseline)					
Raw value	n	175	166	178	171
	Min-max	3-8	1-9	1-9	1-11
	Median	6.0	6.0	6.0	6.0
	Mean (SD)	5.9 (1.30)	5.9 (1.43)	6.0 (1.42)	6.1 (1.46)
	95% CI of mean	5.7, 6.1	5.6, 6.1	5.8, 6.2	5.9, 6.3
First 12 Weeks (Average)					
Change from Baseline	n	175	166	178	171
	95% CI of mean	0.7, 1.1	0.5, 0.8	0.4, 0.7	0.2, 0.5
	SD	1.16	1.06	1.09	1.05
	LS mean	0.9	0.6	0.6	0.5
	95% CI of LS mean	0.8, 1.0	0.5, 0.7	0.5, 0.7	0.3, 0.6
	SE	0.06	0.07	0.06	0.07
	Versus placebo				
	LS mean difference	0.4	0.1	0.1	
	95% CI of LS mean difference	0.3, 0.6	-0.0, 0.3	-0.1, 0.3	
	SE	0.09	0.09	0.09	
	p-Value	<.0001	0.1129	0.1764	

Subscale of sleep quantity ranges from 0 to 24, with score indicating hours of sleep.
Estimates and p-values were from a mixed model and spatial power covariance structure including fixed effects for baseline value, region, treatment, and week.
CI = confidence interval; ITT = intent-to-treat; LS mean = least square mean; Max = maximum; Min = minimum;
N = number of subjects; n = number of subjects in the specified category; SD = standard deviation; SE = standard error.

Table 24. Medical Outcomes Study Sleep Scale-6-Item Sleep Problems Scale: Averaging Across First 12 Weeks (Observed Cases) – ITT Population

Visit		Pregabalin 300 mg N = 177	Pramipexole 0.25 mg N = 169	Pramipexole 0.50 mg N = 178	Placebo N = 174
Week 0 (Baseline)					
Raw value	n	175	168	177	171
	Min-max	7-93	7-87	0-87	3-90
	Median	47.0	47.0	47.0	40.0
	Mean (SD)	45.6 (19.34)	44.7 (18.63)	44.7 (17.89)	43.2 (17.58)
	95% CI of mean	42.7, 48.5	41.9, 47.5	42.0, 47.3	40.5, 45.8
First 12 Weeks (Average)					
Change from Baseline	n	175	168	177	171
	95% CI of mean	-18.8, -13.7	-12.2, -6.7	-13.8, -8.8	-10.4, -5.9
	SD	17.38	17.94	16.86	14.89
	LS mean	-16.5	-10.1	-11.8	-9.3
	95% CI of LS mean	-18.5, -14.5	-12.2, -8.0	-13.8, -9.8	-11.4, -7.3
	SE	1.03	1.05	1.02	1.04
	Versus placebo				
	LS mean difference	-7.2	-0.8	-2.5	
	95% CI of LS mean difference	-10.0, -4.3	-3.7, 2.1	-5.3, 0.4	
	SE	1.46	1.47	1.45	
	p-Value	<0.0001	0.6022	0.0876	

Subscale of 6-item index ranges from 0 to 100 with lower score indicating fewer sleep problems.
Estimates and p-values were from a mixed model and spatial power covariance structure including fixed effects for baseline value, region, treatment, and week.
CI = confidence interval; ITT = intent-to-treat; LS mean = least square mean; Max = maximum; Min = minimum;
N = number of subjects; n = number of subjects in the specified category; SD = standard deviation; SE = standard error.

Table 25. Medical Outcomes Study Sleep Scale-9-Item Sleep Problems Scale: Averaging Across First 12 Weeks (Observed Cases) – ITT Population

Visit		Pregabalin 300 mg N=177	Pramipexole 0.25 mg N=169	Pramipexole 0.50 mg N=178	Placebo N=174
Week 0 (Baseline)					
Raw value	n	175	168	176	171
	Min-max	7-93	7-91	3-87	5-91
	Median	47.0	47.5	47.0	44.0
	Mean (SD)	47.3 (19.17)	46.9 (18.60)	46.0 (17.99)	45.0 (17.73)
	95% CI of mean	44.4, 50.1	44.0, 49.7	43.3, 48.7	42.3, 47.7
First 12 Weeks (Average)					
Change from Baseline	n	175	168	176	171
	95% CI of mean	-19.1, -14.0	-13.1, -7.7	-14.4, -9.3	-10.9, -6.4
	SD	17.14	17.79	17.01	14.92
	LS mean	-16.8	-10.7	-12.5	-9.6
	95% CI of LS mean	-18.9, -14.8	-12.8, -8.7	-14.5, -10.5	-11.6, -7.5
	SE	1.04	1.06	1.03	1.05
	Versus placebo				
	LS mean difference	-7.2	-1.2	-2.9	
	95% CI of LS mean difference	-10.1, -4.4	-4.1, 1.8	-5.8, -0.1	
	SE	1.47	1.49	1.46	
	p-Value	<0.0001	0.4333	0.0454	

Subscale of 9-item index ranges from 0 to 100 with lower score indicating fewer sleep problems.
Estimates and p-values were from a mixed model and spatial power covariance structure including fixed effects for baseline value, region, treatment, and week.
CI = confidence interval; ITT = intent-to-treat; LS mean = least square mean; Max = maximum; Min = minimum; N = number of subjects; n = number of subjects in the specified category; SD = standard deviation; SE = standard error.

Profile of Mood State: POMS data were collected using a subject-rated instrument which comprised 6 subscales and 30 descriptors of mood.

Work Productivity and Activity Impairment Questionnaire-Specific Health Problem (WPAI-SHP): WPAI-SHP percent overall impairment due to health at Week 12 was comparable among treatment groups. Similarly, WPAI-SHP percent activity impairment, percent work time missed, and percent impairment while working due to health were comparable among treatment groups.

Restless Leg Syndrome-Quality of Life (RLS-QoL) Scale: The results from the RLS-QoL scale, averaged across the first 12 weeks for the ITT population, demonstrated greater improvement compared to placebo for the pregabalin 300 mg (LS mean difference=3.85, p=0.0002) and pramipexole 0.50 mg (LS mean difference=2.10, p=0.0377) treatment groups but not for the pramipexole 0.25 mg treatment group (Table 26).

Table 26. Restless Legs Syndrome-Quality of Life Summary Score: Averaging Across First 12 Weeks (Observed Cases) – ITT Population

Visit		Pregabalin 300 mg N=177	Pramipexole 0.25 mg N=169	Pramipexole 0.50 mg N=178	Placebo N=174
Week 0 (Baseline)					
Raw value	n	173	169	176	168
	Min-max	27.5-95.0	22.5-95.0	25.0-97.5	7.5-90.0
	Median	69.40	67.50	70.00	70.00
	Mean (SD)	67.72 (13.841)	65.77 (15.900)	66.37 (14.553)	67.21 (15.426)
	95% CI of mean	65.64, 69.79	63.36, 68.19	64.21, 68.54	64.86, 69.56
First 12 Weeks (Average)					
Change from Baseline	n	173	169	176	168
	95% CI of mean	8.17, 11.90	5.75, 9.37	7.35, 10.87	4.26, 7.78
	SD	12.428	11.920	11.818	11.547
	LS mean	10.93	7.54	9.18	7.08
	95% CI of LS mean	9.53, 12.33	6.12, 8.95	7.80, 10.56	5.66, 8.50
	SE	0.713	0.721	0.704	0.724
	Versus placebo				
	LS mean difference	3.85	0.45	2.10	
	95% CI of LS mean difference	1.86, 5.83	-1.54, 2.45	0.12, 4.07	
	SE	1.011	1.019	1.007	
	p-Value	0.0002	0.6553	0.0377	

Summary total score ranges from 0 to 100 hours. Higher score indicates better quality of life.
Estimates and p-values were from a mixed model and spatial power covariance structure including fixed effects for baseline value, region, treatment, and week.
CI = confidence interval; ITT = intent-to-treat; LS mean = least square mean; Max = maximum; Min = minimum; N = number of subjects; n = number of subjects in the specified category; SD = standard deviation; SE = standard error.

Medical Outcomes Study-Short Form 36: The results of the MOS-SF 36, averaged across the first 12 weeks for the ITT population, were included in the gatekeeping procedure used to protect Type I error.

The pregabalin-treated group demonstrated nominally statistically significant improvement in bodily pain ($p<0.0001$; Table 27) and physical role summary ($p<0.0065$; Table 28.

Table 27. Medical Outcomes Study-Short Form 36 – Bodily Pain: Averaging Across First 12 Weeks (Observed Cases) – ITT Population

Visit		Pregabalin 300 mg N=177	Pramipexole 0.25 mg N=169	Pramipexole 0.50 mg N=178	Placebo N=174
Week 0 (Baseline)					
Raw value	n	175	168	177	171
	Min-max	0-100	0-100	10-100	12-100
	Median	61.0	51.5	61.0	61.0
	Mean (SD)	61.6 (24.40)	58.1 (23.42)	60.1 (23.44)	61.9 (22.57)
	95% CI of mean	58.0, 65.2	54.5, 61.7	56.6, 63.6	58.5, 65.4
First 12 Weeks (Average)					
Change from Baseline	n	175	168	177	171
	95% CI of mean	8.3, 15.1	3.7, 10.5	5.5, 11.9	0.8, 6.4
	SD	22.68	22.53	21.46	18.33
	LS mean	13.5	6.5	9.1	4.9
	95% CI of LS mean	11.1, 15.8	4.1, 8.9	6.7, 11.4	2.5, 7.3
	SE	1.20	1.22	1.19	1.22
	Versus placebo				
	LS mean difference	8.6	1.6	4.2	
	95% CI of LS mean difference	5.3, 11.9	-1.7, 5.0	0.9, 7.5	
	SE	1.70	1.72	1.69	
	p-Value	<0.0001	0.3429	0.0135	

Subscale bodily pain ranges from 0 to 100 with higher score indicating less bodily pain. Estimates and p-values were from a mixed model and spatial power covariance structure including fixed effects for baseline value, region, treatment, and week.
CI = confidence interval; ITT = intent-to-treat; LS mean = least square mean; Max = maximum; Min = minimum;
N = number of subjects; n = number of subjects in the specified category; SD = standard deviation; SE = standard error.

Table 28. Medical Outcomes Study-Short Form 36 – Summary Physical Score: Averaging Across First 12 Weeks (Observed Cases) – ITT Population

Visit		Pregabalin 300 mg N = 177	Pramipexole 0.25 mg N = 169	Pramipexole 0.50 mg N = 178	Placebo N = 174
Week 0 (Baseline)					
Raw value	n	174	167	176	170
	Min-max	17-100	24-100	18-100	15-100
	Median	76.7	72.4	75.1	78.3
	Mean (SD)	72.9	71.6	71.4	73.6
	95% CI of mean	70.2, 75.7	68.9, 74.3	68.8, 73.9	70.9, 76.3
First 12 Weeks (Average)					
Change from Baseline	n	174	167	176	170
	95% CI of mean	3.2, 6.7	0.6, 4.7	2.1, 5.4	0.5, 3.7
	SD	11.71	13.43	11.18	10.52
	LS mean	5.6	2.9	3.8	2.7
	95% CI of LS mean	4.1, 7.0	1.4, 4.3	2.4, 5.2	1.2, 4.2
	SE	0.74	0.76	0.73	0.75
	Versus placebo				
	LS mean difference	2.9	0.1	1.1	
	95% CI of LS mean difference	0.8, 4.9	-1.9, 2.2	-1.0, 3.1	
	SE	1.05	1.06	1.05	
	p-Value	0.0065	0.8877	0.2995	

Subscale of summary physical score ranges from 0 to 100 with higher score indicating better physical condition. Estimates and p-values were from a mixed model and spatial power covariance structure including fixed effects for baseline value, region, treatment, and week.
CI = confidence interval; ITT = intent-to-treat; LS mean = least square mean; Max = maximum; Min = minimum; N = number of subjects; n = number of subjects in the specified category; SD = standard deviation; SE = standard error.

The following MOS-SF 36 subscales as physical functioning, physical role, general health, social functioning, emotional role, mental health and mental health summary did not demonstrate considerable changes for any of the treatment groups when analyzed by week, averaged across the first 12 weeks, and for Week 12 with LOCF.

Work Productivity and Activity Impairment Questionnaire; Specific Health Problem (WPAI-SHP): The WPAI-SHP for percent overall work impairment due to health, percent activity impairment due to health and percent work time missed due to health is summarized in (Table 29).

Table 29. Work Productivity and Activity Impairment Questionnaire; Specific Health Problem: Raw Value and Change From Baseline - Using Mixed Model and Spatial Power Covariance Structure - at Week 12 (Observed Cases) – ITT Population

Visit		Pregabalin 300 mg N=177	Pramipexole 0.25 mg N=169	Pramipexole 0.50 mg N=178	Placebo N=174
Percent Overall Work Impairment					
Week 0 (Baseline)					
Raw value	n	13	9	16	13
	Min-max	0-40	0-50	0-60	0-70
	Median	20.0	10.0	35.0	30.0
	Mean (SD)	17.7 (15.89)	13.3 (15.81)	30.6 (23.80)	26.2 (23.29)
	95% CI of mean	8.1, 27.3	1.2, 25.5	17.9, 43.3	12.1, 40.2
First 12 Weeks (Average)					
Change from Baseline	n	9	4	10	9
	95% CI of mean	-21.5, 1.5	-14.2, 4.2	-36.0, 4.0	-25.4, 4.6
	SD	15.00	5.77	27.97	19.53
	LS mean	-10.4	-10.3	-14.5	-7.0
	95% CI of LS mean	-21.8, 1.1	-28.3, 7.7	-25.3, -3.7	-18.2, 4.3
	SE	5.58	8.76	5.25	5.46
	Versus placebo				
	LS mean difference	-3.4	-3.3	-7.6	
	95% CI of LS mean difference	-19.6, 12.8	-24.9, 18.2	-23.0, 7.8	
	SE	7.86	10.49	7.50	
	p-Value	0.6686	0.7521	0.3210	
Percent Activity Impairment					
Week 0 (Baseline)					
Raw value	n	26	27	33	29
	Min-max	0-90	0-80	0-80	0-100
	Median	35.0	30.0	40.0	30.0
	Mean (SD)	37.7 (28.3)	32.6 (21.94)	36.7 (21.60)	38.3 (32.85)
	95% CI of mean	26.3, 49.1	23.9, 41.3	29.0, 44.3	25.8, 50.8
First 12 Weeks (Average)					
Change from Baseline	n	18	22	25	20
	95% CI of mean	-33.3, -7.9	-24.0, 0.4	-27.9, -7.3	-17.4, -0.6
	SD	25.55	27.54	25.05	18.04
	LS mean	-20.9	-13.5	-16.6	-9.8
	95% CI of LS mean	-29.8, -11.9	-21.6, -5.4	-24.3, -8.9	-18.3, -1.3
	SE	4.49	4.06	3.88	4.26
	Versus placebo				
	LS mean difference	-11.1	-3.7	-6.8	
	95% CI of LS mean difference	-23.4, 1.2	-15.4, 8.0	-18.4, 4.8	
	SE	6.18	5.89	5.81	
	p-Value	0.7666	0.5286	0.2444	
Percent Work Time Missed					
Week 0 (Baseline)					
Raw value	n	13	9	16	13
	Min-max	0-0	0-0	0-0	0-0
	Median	0.0	0.0	0.0	0.0
	Mean (SD)	0.0 (0.00)	0.0 (0.00)	0.0 (0.00)	0.0 (0.00)
	95% CI of mean	0.0, 0.0	0.0, 0.0	0.0, 0.0	0.0, 0.0
First 12 Weeks (Average)					
Change from Baseline	n	9	4	10	9

Table 29. Work Productivity and Activity Impairment Questionnaire; Specific Health Problem: Raw Value and Change From Baseline - Using Mixed Model and Spatial Power Covariance Structure - at Week 12 (Observed Cases) – ITT Population

Visit		Pregabalin 300 mg N=177	Pramipexole 0.25 mg N=169	Pramipexole 0.50 mg N=178	Placebo N=174
	95% CI of mean	0.0, 0.0	0.0, 0.0	0.0, 0.0	-1.2, 4.6
	SD	0.00	0.00	0.00	3.80
	LS mean	-0.2	-0.2	0.1	1.7
	95% CI of LS mean	-1.6, 1.2	-2.3, 1.9	-1.2, 1.4	0.3, 3.0
	SE	0.68	1.02	0.64	0.67
	Versus placebo				
	LS mean difference	-1.8	-1.9	-1.6	
	95% CI of LS mean difference	-3.8, 0.1	-4.4, 0.6	-3.5, 0.3	
	SE	0.95	1.22	0.93	
	p-Value	0.0676	0.1322	0.1044	

Subscale of summary physical score ranges from 0 to 100 with higher score indicating better physical condition. Estimates and p-values were from a mixed model and spatial power covariance structure including fixed effects for baseline value, region, treatment, and week.
CI = confidence interval; ITT = intent-to-treat; LS mean = least square mean; Max = maximum; Min = minimum; N = number of subjects; n = number of subjects in the specified category; SD = standard deviation; SE = standard error.

Safety Results: An overview of treatment-emergent AEs is given in Table 30. The number of subjects experiencing at least 1 treatment-emergent AE was comparable among the 6 treatment arms.

Nine (4.9%), 12 (6.7%), 9 (5.0%), 5 (8.5%), and 2 (3.4%) subjects experienced treatment-emergent SAEs during pregabalin 300 mg, pramipexole 0.25 mg, pramipexole 0.50 mg, placebo to pregabalin 300 mg, and placebo to pramipexole 0.25 mg treatment, respectively (Table 30).

Twenty-one (11.5%), 24 (13.5%), 23 (12.8%), 11 (18.6%), 7 (11.9%), and 9 (14.8%) subjects experienced treatment-emergent severe AEs during pregabalin 300 mg, pramipexole 0.25 mg, pramipexole 0.50 mg, placebo to pregabalin 300 mg, placebo to pramipexole 0.25 mg, and placebo to pramipexole 0.50 mg treatment, respectively (Table 30).

Table 30. Summary of Treatment-Emergent Adverse Events, All Causality and Treatment Related

Number (%) of subjects	Pregabalin 300 mg	Pramipexole 0.25 mg	Pramipexole 0.50 mg	Placebo to Pregabalin 300 mg	Placebo to Pramipexole 0.25 mg	Placebo to Pramipexole 0.50 mg
All Causality						
Number of subjects evaluable for AEs	182	178	180	59	59	61
Number of AEs	616	537	583	227	179	186
Subjects with AEs	155 (85.2)	142 (79.8)	140 (77.8)	52 (88.1)	46 (78.0)	48 (78.7)
Subjects with SAEs	9 (4.9)	12 (6.7)	9 (5.0)	5 (8.5)	2 (3.4)	0
Subjects with severe AEs	21 (11.5)	24 (13.5)	23 (12.8)	11 (18.6)	7 (11.9)	9 (14.8)
Subjects discontinued due to AEs	50 (27.5)	33 (18.5)	43 (23.9)	17 (28.8)	9 (15.3)	8 (13.1)
Subjects with dose reduced or temporary discontinuation due to AEs	6 (3.3)	8 (4.5)	5 (2.8)	3 (5.1)	3 (5.1)	4 (6.6)
Treatment Related						
Number of subjects evaluable for AEs	182	178	180	59	59	61
Number of AEs	355	238	270	111	58	53
Subjects with AEs	120 (65.9)	89 (50.0)	102 (56.7)	30 (50.8)	26 (44.1)	28 (45.9)
Subjects with SAEs	2 (1.1)	3 (1.7)	1 (0.6)	1 (1.7)	0	0
Subjects with severe AEs	13 (7.1)	8 (4.5)	14 (7.8)	6 (10.2)	3 (5.1)	4 (6.6)
Subjects discontinued due to AEs	42 (23.1)	24 (13.5)	31 (17.2)	13 (22.0)	6 (10.2)	7 (11.5)
Subjects with dose reduced or temporary discontinuation due to AEs	4 (2.2)	4 (2.2)	3 (1.7)	1 (1.7)	1 (1.7)	0

Results included data up to 999 days after last dose of study drug.
Except for the number of AEs, subjects were counted only once per treatment in each row.
SAEs – according to the Investigator's assessment.
MedDRA (Version 14.0) coding was applied.
AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; SAE = serious adverse event.

All Causality Adverse Events: A summary of all causality treatment-emergent AEs occurring in at least 5% of the subjects during any treatment period is shown in Table 31. The most frequently reported all causality treatment-emergent AEs during pregabalin 300 mg treatment were dizziness, somnolence, fatigue, headache and nasopharyngitis. The most frequently reported AEs during pramipexole 0.25 mg treatment were headache, nasopharyngitis, fatigue, and nausea. The most frequently reported AEs during pramipexole 0.50 mg treatment were headache, nausea, and fatigue. The most frequently reported treatment-emergent AEs during placebo to pregabalin 300 mg treatment were dizziness, headache, somnolence, and fatigue. The most frequently reported AEs during placebo to pramipexole 0.25 mg treatment were influenza, weight increase, dizziness, and headache. The most frequently reported AEs during placebo pramipexole 0.50 mg treatment were headache, nasopharyngitis, fatigue, and influenza.

Table 31. Treatment-Emergent Non Serious Adverse Events by System Organ Class and Preferred Term (All Causalities) For Events Having a Frequency Rate ≥5

	Pregabalin 300 mg n (%)	Pramipexole 0.25 mg n (%)	Pramipexole 0.50 mg n (%)	Placebo to Pregabalin 300 mg n (%)	Placebo to Pramipexole 0.25 mg n (%)	Placebo to Pramipexole 0.50 mg n (%)
Number % of Subjects						
Evaluable for Adverse Events	**182**	**178**	**180**	**59**	**59**	**61**
With adverse Events	**134 (73.6)**	**110 (61.8)**	**118 (65.6)**	**42 (71.2)**	**34 (57.6)**	**41 (67.2)**
Number (%) of Subjects With Adverse Events by: System Organ Class and MedDRA (v14.0) Preferred Term						
Ear and labyrinth disorders	13 (7.1)	2 (1.1)	5 (2.8)	3 (5.1)	0	0
Vertigo	13 (7.1)	2 (1.1)	5 (2.8)	3 (5.1)	0	0
Eye disorders	3 (1.6)	4 (2.2)	1 (0.6)	3 (5.1)	1 (1.7)	0
Vision blurred	3 (1.6)	4 (2.2)	1 (0.6)	3 (5.1)	1 (1.7)	0
Gastrointestinal disorders	37 (20.3)	36 (20.2)	49 (27.2)	11 (18.6)	9 (15.3)	12 (19.7)
Abdominal pain upper	5 (2.7)	9 (5.1)	5 (2.8)	4 (6.8)	1 (1.7)	3 (4.9)
Constipation	14 (7.7)	3 (1.7)	2 (1.1)	5 (8.5)	1 (1.7)	0
Diarrhoea	7 (3.8)	9 (5.1)	10 (5.6)	2 (3.4)	5 (8.5)	5 (8.2)
Dry mouth	9 (4.9)	4 (2.2)	14 (7.8)	2 (3.4)	1 (1.7)	2 (3.3)
Nausea	11 (6.0)	18 (10.1)	26 (14.4)	3 (5.1)	3 (5.1)	4 (6.6)
Vomiting	3 (1.6)	4 (2.2)	10 (5.6)	3 (5.1)	2 (3.4)	5 (8.2)
General disorders and administration site conditions	37 (20.3)	30 (16.9)	28 (15.6)	9 (15.3)	8 (13.6)	10 (16.4)
Fatigue	23 (12.6)	19 (10.7)	22 (12.2)	7 (11.9)	5 (8.5)	8 (13.1)
Irritability	5 (2.7)	9 (5.1)	2 (1.1)	2 (3.4)	1 (1.7)	1 (1.6)
Oedema peripheral	12 (6.6)	4 (2.2)	6 (3.3)	1 (1.7)	2 (3.4)	1 (1.6)
Infections and infestations	40 (22.0)	40 (22.5)	27 (15.0)	12 (20.3)	13 (22.0)	19 (31.1)
Cystitis	3 (1.6)	4 (2.2)	0	1 (1.7)	1 (1.7)	4 (6.6)
Influenza	9 (4.9)	13 (7.3)	3 (1.7)	4 (6.8)	8 (13.6)	7 (11.5)
Nasopharyngitis	19 (10.4)	20 (11.2)	17 (9.4)	3 (5.1)	3 (5.1)	9 (14.8)
Sinusitis	6 (3.3)	3 (1.7)	4 (2.2)	4 (6.8)	4 (6.8)	0
Urinary tract infection	6 (3.3)	2 (1.1)	6 (3.3)	3 (5.1)	3 (5.1)	2 (3.3)
Investigations	16 (8.8)	12 (6.7)	12 (6.7)	2 (3.4)	7 (11.9)	4 (6.6)
Weight increased	16 (8.8)	12 (6.7)	12 (6.7)	2 (3.4)	7 (11.9)	4 (6.6)
Musculoskeletal and connective tissue disorders	26 (14.3)	28 (15.7)	29 (16.1)	7 (11.9)	11 (18.6)	8 (13.1)
Arthralgia	7 (3.8)	9 (5.1)	8 (4.4)	1 (1.7)	3 (5.1)	4 (6.6)
Back pain	10 (5.5)	15 (8.4)	13 (7.2)	2 (3.4)	4 (6.8)	4 (6.6)
Musculoskeletal pain	5 (2.7)	4 (2.2)	4 (2.2)	1 (1.7)	3 (5.1)	2 (3.3)
Pain in extremity	7 (3.8)	7 (3.9)	7 (3.9)	4 (6.8)	2 (3.4)	1 (1.6)
Nervous system disorders	76 (41.8)	52 (29.2)	52 (28.9)	22 (37.3)	12 (20.3)	17 (27.9)

Table 31. Treatment-Emergent Non Serious Adverse Events by System Organ Class and Preferred Term (All Causalities) For Events Having a Frequency Rate ≥5

	Pregabalin 300 mg n (%)	Pramipexole 0.25 mg n (%)	Pramipexole 0.50 mg n (%)	Placebo to Pregabalin 300 mg n (%)	Placebo to Pramipexole 0.25 mg n (%)	Placebo to Pramipexole 0.50 mg n (%)
Balance disorder	2 (1.1)	2 (1.1)	1 (0.6)	4 (6.8)	0	0
Dizziness	39 (21.4)	15 (8.4)	17 (9.4)	10 (16.9)	6 (10.2)	3 (4.9)
Headache	22 (12.1)	30 (16.9)	35 (19.4)	9 (15.3)	6 (10.2)	12 (19.7)
Paraesthesia	5 (2.7)	4 (2.2)	3 (1.7)	3 (5.1)	1 (1.7)	0
Somnolence	32 (17.6)	12 (6.7)	14 (7.8)	7 (11.9)	4 (6.8)	5 (8.2)
Psychiatric disorders	10 (5.5)	4 (2.2)	7 (3.9)	3 (5.1)	2 (3.4)	2 (3.3)
Depression	10 (5.5)	4 (2.2)	7 (3.9)	3 (5.1)	2 (3.4)	2 (3.3)
Respiratory, thoracic and mediastinal disorders	4 (2.2)	7 (3.9)	7 (3.9)	0	4 (6.8)	1 (1.6)
Cough	4 (2.2)	7 (3.9)	7 (3.9)	0	4 (6.8)	1 (1.6)
Vascular disorders	8 (4.4)	6 (3.4)	4 (2.2)	4 (6.8)	3 (5.1)	2 (3.3)
Hypertension	7 (3.8)	6 (3.4)	4 (2.2)	1 (1.7)	3 (5.1)	2 (3.3)
Orthostatic hypotension	1 (0.5)	0	0	3 (5.1)	0	0

Subjects are only counted once per treatment for each row.
Includes data up to 999 days after last dose of study drug.
MedDRA (v14.0) coding dictionary applied.
MedDRA = Medical dictionary for Regulatory activities; n = number of subjects; v = version.

Treatment-Related Adverse Events: A summary of treatment-emergent AEs considered related to treatment by the Investigator occurring in at least 5% of the subjects during any treatment period is shown in Table 32. The most frequently reported treatment related treatment-emergent AEs during pregabalin 300 mg treatment were dizziness, somnolence, fatigue, and headache. The most frequently reported AEs during pramipexole 0.25 mg treatment were headache, fatigue, nausea, and dizziness. The most frequently reported AEs during pramipexole 0.50 mg treatment were nausea, headache, and fatigue. The most frequently reported treatment-emergent AEs during placebo to pregabalin 300 mg treatment were headache, dizziness, somnolence, and fatigue. The most frequently reported AEs during placebo to pramipexole 0.25 mg treatment were weight increase, dizziness, fatigue, and headache. The most frequently reported AEs during placebo pramipexole 0.50 mg treatment were headache and fatigue.

Table 32. Incidence of Treatment Related Treatment-Emergent Adverse Events in ≥5 Subjects for Any Treatment Per Preferred Term

Number (%) of subjects with AE by: System organ class and MedDRA (version 14.0) preferred term	Pregabalin 300 mg N=182	Pramipexole 0.25 mg N=178	Pramipexole 0.50 mg N=180	Placebo to Pregabalin 300 mg N=59	Placebo to Pramipexole 0.25 mg N=59	Placebo to Pramipexole 0.50 mg N=61
Ear and labyrinth disorders	14 (7.7)	1 (0.6)	4 (2.2)	3 (5.1)	0	0
Vertigo	13 (7.1)	1 (0.6)	4 (2.2)	2 (3.4)	0	0
Gastrointestinal disorders	30 (16.5)	27 (15.2)	43 (23.9)	8 (13.6)	6 (10.2)	6 (9.8)
Abdominal pain upper	3 (1.6)	6 (3.4)	5 (2.8)	1 (1.7)	1 (1.7)	0
Constipation	11 (6.0)	3 (1.7)	2 (1.1)	4 (6.8)	0	0
Dry mouth	9 (4.9)	3 (1.7)	11 (6.1)	2 (3.4)	1 (1.7)	2 (3.3)
Nausea	11 (6.0)	14 (7.9)	23 (12.8)	3 (5.1)	3 (5.1)	2 (3.3)
General disorders and administrative site conditions	39 (21.4)	31 (17.4)	33 (18.3)	10 (16.9)	6 (10.2)	10 (16.4)
Fatigue	22 (12.1)	16 (9.0)	19 (10.6)	7 (11.9)	5 (8.5)	5 (8.2)
Irritability	5 (2.7)	6 (3.4)	2 (1.1)	1 (1.7)	0	1 (1.6)
Oedema peripheral	9 (4.9)	3 (1.7)	3 (1.7)	0	1 (1.7)	0
Investigations	18 (9.9)	13 (7.3)	16 (8.9)	4 (6.8)	7 (11.9)	2 (3.3)
Weight increased	16 (8.8)	9 (5.1)	11 (6.1)	2 (3.4)	6 (10.2)	2 (3.3)
Nervous system disorders	79 (43.4)	46 (25.8)	51 (28.3)	20 (33.9)	12 (20.3)	14 (23.0)
Dizziness	37 (20.3)	14 (7.9)	12 (6.7)	8 (13.6)	5 (8.5)	3 (4.9)
Headache	17 (9.3)	17 (9.6)	21 (11.7)	9 (15.3)	5 (8.5)	7 (11.5)
Memory impairment	6 (3.3)	1 (0.6)	1 (0.6)	1 (1.7)	0	1 (1.6)
Somnolence	30 (16.5)	9 (5.1)	13 (7.2)	7 (11.9)	3 (5.1)	4 (6.6)
Psychiatric disorders	26 (14.3)	20 (11.2)	21 (11.7)	9 (15.3)	7 (11.9)	4 (6.6)
Depression	6 (3.3)	3 (1.7)	4 (2.2)	2 (3.4)	1(1.7)	2 (3.3)
Insomnia	6 (3.3)	5 (2.8)	3 (1.7)	1 (1.7)	2 (3.4)	1 (1.6)

Subjects were counted only once per treatment in each row.
Results included data up to 999 days after last dose of study drug.
MedDRA (Version 14.0) coding was applied.
AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; N = Number of subjects evaluable for AEs.

Treatment-Emergent Serious Adverse Events: Treatment emergent SAEs Table 33 were reported in 9 (4.9%) subjects during pregabalin 300 mg treatment, 12 (6.7%) subjects during pramipexole 0.25 mg treatment, 9 (5.0%) subjects during pramipexole 0.50 mg treatment, 5 (8.5%) subjects during placebo to pregabalin 300 mg treatment, and 2 (3.4%) subjects during placebo to pramipexole 0.25 mg treatment.

Table 33. Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term (All Causalities) For Events Having a Frequency Rate ≥0

	Pregabalin 300 mg n (%)	Pramipexole 0.25 mg n (%)	Pramipexole 0.50 mg n (%)	Placebo to Pregabalin 300 mg n (%)	Placebo to Pramipexole 0.25 mg n (%)	Placebo to Pramipexole 0.50 mg n (%)
Number % of Subjects						
Evaluable for Adverse Events	**182**	**178**	**180**	**59**	**59**	**61**
With adverse Events	**9 (4.9)**	**12 (6.7)**	**9 (5.0)**	**5 (8.5)**	**2 (3.4)**	**0**
Number (%) of Subjects With Adverse Events by: System Organ Class and MedDRA (v14.0) Preferred Term						
Cardiac disorders	1 (0.5)	1 (0.6)	2 (1.1)	0	0	0
Acute myocardial infarction	1 (0.5)	0	0	0	0	0
Angina pectoris	0	1 (0.6)	0	0	0	0
Atrial fibrillation	0	0	1 (0.6)	0	0	0
Bradyarrhythmia	0	0	1 (0.6)	0	0	0
Eye disorders	0	0	1 (0.6)	0	0	0
Amaurosis fugax	0	0	1 (0.6)	0	0	0
Gastrointestinal disorders	1 (0.5)	0	0	0	0	0
Pancreatitis acute	1 (0.5)	0	0	0	0	0
General disorders and administration site conditions	0	3 (1.7)	0	0	0	0
Chest pain	0	2 (1.1)	0	0	0	0
Device dislocation	0	1 (0.6)	0	0	0	0
Hepatobiliary disorders	1 (0.5)	0	0	1 (1.7)	0	0
Cholecystitis acute	0	0	0	1 (1.7)	0	0
Hepatitis acute	1 (0.5)	0	0	0	0	0
Immune system disorders	0	1 (0.6)	0	0	0	0
Allergy to arthropod sting	0	1 (0.6)	0	0	0	0
Infections and infestations	0	0	1 (0.6)	0	0	0
Pneumonia	0	0	1 (0.6)	0	0	0
Injury, poisoning and procedural complications	3 (1.6)	2 (1.1)	2 (1.1)	0	0	0
Ankle fracture	1 (0.5)	0	0	0	0	0
Fall	0	1 (0.6)	2 (1.1)	0	0	0
Fractured coccyx	0	1 (0.6)	0	0	0	0
Hand fracture	0	0	1 (0.6)	0	0	0
Rib fracture	1 (0.5)	0	0	0	0	0
Tendon rupture	0	1 (0.6)	0	0	0	0
Tibia fracture	0	0	1 (0.6)	0	0	0
Wound	1 (0.5)	0	0	0	0	0
Musculoskeletal and connective tissue disorders	1 (0.5)	1 (0.6)	1 (0.6)	0	0	0

Table 33. Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term (All Causalities) For Events Having a Frequency Rate ≥0

	Pregabalin 300 mg n (%)	Pramipexole 0.25 mg n (%)	Pramipexole 0.50 mg n (%)	Placebo to Pregabalin 300 mg n (%)	Placebo to Pramipexole 0.25 mg n (%)	Placebo to Pramipexole 0.50 mg n (%)
Back pain	0	1 (0.6)	0	0	0	0
Intervertebral disc protrusion	0	0	1 (0.6)	0	0	0
Osteoarthritis	1 (0.5)	0	0	0	0	0
Spinal osteoarthritis	0	0	1 (0.6)	0	0	0
Neoplasms benign, malignant and unspecified (inclusive cysts and polyps)	0	1 (0.6)	1 (0.6)	1 (1.7)	0	0
Breast cancer	0	0	1 (0.6)	1 (1.7)	0	0
Gastric cancer	0	1 (0.6)	0	0	0	0
Nervous system disorders	2 (1.1)	3 (1.7)	0	1 (1.7)	1 (1.7)	0
Carotid artery stenosis	0	1 (0.6)	0	0	0	0
Cerebrovascular accident	0	1 (0.6)	0	1 (1.7)	0	0
Loss of consciousness	0	1 (0.6)	0	0	0	0
Multiple sclerosis	0	0	0	0	1 (1.7)	0
Neurological symptom	0	1 (0.6)	0	0	0	0
Syncope	1 (0.5)	0	0	0	0	0
Transient ischaemic attack	1 (0.5)	0	0	0	0	0
Psychiatric disorders	1 (0.5)	0	0	2 (3.4)	0	0
Mental status changes	1 (0.5)	0	0	0	0	0
Suicidal ideation	0	0	0	1 (1.7)	0	0
Withdrawal syndrome	0	0	0	1 (1.7)	0	0
Renal and urinary disorders	0	1 (0.6)	1 (0.6)	0	0	0
Bladder dysplasia	0	1 (0.6)	0	0	0	0
Urinary retention	0	0	1 (0.6)	0	0	0
Reproductive system and breast disorders	0	1 (0.6)	0	0	0	0
Benign prostatic hyperplasia	0	1 (0.6)	0	0	0	0
Respiratory, thoracic and mediastinal disorders	0	1 (0.6)	0	0	0	0
Dyspnoea	0	1 (0.6)	0	0	0	0
Surgical and medical procedures	0	1 (0.6)	0	0	1 (1. 7	0
Bladder calculus removal	0	1 (0.6)	0	0	0	0
Spinal deformity correction	0	0	0	0	1 (1. 7)	0
Vascular disorders	1 (0.5)	1 (0.6)	0	0	0	0
Deep vein thrombosis	1 (0.5)	0	0	0	0	0
Hypertension	0	1 (0.6)	0	0	0	0

Table 33. Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term (All Causalities) For Events Having a Frequency Rate ≥0

	Pregabalin 300 mg n (%)	Pramipexole 0.25 mg n (%)	Pramipexole 0.50 mg n (%)	Placebo to Pregabalin 300 mg n (%)	Placebo to Pramipexole 0.25 mg n (%)	Placebo to Pramipexole 0.50 mg n (%)

Subjects are only counted once per treatment for each row.
Includes data up to 999 days after last dose of study drug.
MedDRA (v14.0) coding dictionary applied.
MedDRA = Medical dictionary for Regulatory Activities; n = number of subjects; v = version.

Treatment Related Serious Adverse Events: Treatment related SAEs Table 34 were reported in 9 (4.9%) subjects during pregabalin 300 mg treatment, 12 (6.7%) subjects during pramipexole 0.25 mg treatment, 9 (5.0%) subjects during pramipexole 0.50 mg treatment, 5 (8.5%) subjects during placebo to pregabalin 300 mg treatment, and 2 (3.4%) subjects during placebo to pramipexole 0.25 mg treatment. Two (1.1%) subjects during pregabalin 300 mg treatment, 3 (1.7%) subjects during pramipexole 0.25 mg treatment, 1 (0.6%) subject during pramipexole 0.50 mg treatment, and 1 (1.7%) subject during placebo to pregabalin 300 mg treatment reported SAEs that were considered treatment related.

Table 34. Treatment-Related Serious Adverse Events

Suspect Drug/Dose	Verbatim Term/MedDRA Preferred Term	Therapy Stop Date	Event Start Day/ Stop Day	Action Taken	Causality	Outcome
Pregabalin 300 mg						
Pregabalin 300 mg	Altered mental status/mental status changes	245	209/246	Permanently withdrawn	Related	Recovered/resolved
Pregabalin 75 mg	Syncope/syncope	2	2/3	Permanently withdrawn	Related	Recovered/resolved
Pramipexole 0.25 mg						
Pramipexole 2HCl	Chest pain/chest pain	47	11/11	Permanently withdrawn	Related	Recovered/resolved
	Worsening of hypertension/hypertension	47	11/32	Permanently withdrawn	Related	Recovered/resolved
Pramipexole 2HCl 0.25 mg	unconsciousness with amnesia/ loss of consciousness	266	86/90	Dose not changed	Related	Recovered/resolved with sequel
	fracture of coccyx/spinal cord injury	266	86/90	Dose not changed	Related	Recovered/resolved with sequel
Pramipexole 2HCl 0.25 mg	Bilateral atypical neurological symptoms like paresthesia face and limbs bilateral/neurological symptom	77	14/14	Dose not changed	Related	Recovered/resolved
Pramipexole 0.50 mg/0.50 mg						
Pramipexole 2 HCl 0.50 mg	Bradyarrhythmia/bradyarrhythmia	273	213/217	Dose not changed	Related	Recovered/resolved
Placebo to Pregabalin 300 mg						
Pregabalin/75.00 mg	Withdrawal syndrome/withdrawal syndrome	365	360/367	Dose not changed	Related	Recovered/resolved

MedDRA (Version 14.0) coding was applied.
ID = identification; MedDRA = Medical Dictionary for Regulatory Activities; SAE = serious adverse event.

Other Observations Related to Safety:

Suicidality: Table 35 summarizes the results of the Columbia Classification Algorithm of Suicide Assessment (C-CASA). None of the subjects reported suicide attempts or suicidal ideation at Baseline.

Table 35. Columbia Classification Algorithm of Suicide Assessment (C-CASA)

C-CASA Category	Pregabalin 300 mg N=182 n (%)	Pramipexole 0.25 mg N=178 n (%)	Pramipexole 0.50 mg N=180 n (%)	Placebo to Pregabalin 300 mg N=59 n (%)	Placebo to Pramipexole 0.25 mg N=59 n (%)	Placebo to Pramipexole 0.50 mg N=61 n (%)
Screening (lifetime)						
Number assessed	182	178	180	59	59	61
Completed suicide	0	0	0	0	0	0
Suicide attempt	3 (1.6)	2 (1.1)	2 (1.1)	0	0	0
Preparatory acts towards imminent suicidal behavior	1 (<1.0)	0	1 (<1.0)	1 (1.7)	1 (1.7)	0
Suicidal ideation	9 (4.9)	8 (4.5)	7 (3.9)	5 (8.5)	4 (6.8)	0
Self injurious behavior, no suicidal intent	1 (<1.0)	0	1 (<1.0)	0	0	0
Baseline						
Number assessed	182	178	180	59	59	61
Completed suicide	0	0	0	0	0	0
Suicide attempt	0	0	0	0	0	0
Preparatory acts towards imminent suicidal behavior	0	0	0	0	0	0
Suicidal ideation	0	0	0	0	0	0
Self injurious behavior, no suicidal intent	0	0	0	0	0	0
Postbaseline						
Number assessed	176	169	178	59	58	57
Completed suicide	0	0	0	0	0	0
Suicide attempt	0	0	0	0	0	0
Preparatory acts towards imminent suicidal behavior	0	0	0	1 (1.7)	0	0
Suicidal ideation	2 (1.1)	3 (1.8)	2 (1.1)	4 (6.8)	0	0
Self injurious behavior, no suicidal intent	0	0	0	0	0	0

C-CASA = Columbia Classification Algorithm of Suicide Assessment; N = total number of subjects that received the treatment; n = number of subjects returning a positive response.

Permanent Discontinuations due to Adverse Events: Table 36 presents the permanent discontinuations due to AEs, summarized by SOC and preferred term. The most frequently reported AEs leading to discontinuations were somnolence (17 subjects), dizziness (13 subjects), headache (9 subjects), nausea (9 subjects), increase in weight (7 subjects), and fatigue (7 subjects).

Table 36. Discontinuations due to Adverse Events in ≥2 Subjects for any Treatment Per Preferred Term

Number (%) of Subjects With AE by: MedDRA (version 14.0) preferred term	Pregabalin 300 mg N=182	Pramipexole 0.25 mg N=178	Pramipexole 0.50 mg N=180	Placebo to Pregabalin 300 mg N=59	Placebo to Pramipexole 0.25 mg N=59	Placebo to Pramipexole 0.50 mg N=61
Vertigo	2 (1.1)	0	1 (0.6)	0	0	0
Abdominal pain upper	1 (0.5)	1 (0.6)	4 (2.2)	0	0	0
Nausea	0	3 (1.7)	5 (2.8)	0	1 (1.7)	0
Fatigue	1 (0.5)	2 (1.1)	2 (1.1)	2 (3.4)	0	0
Weight increased	2 (1.1)	3 (1.7)	1 (0.6)	1 (1.7)	0	0
Pain in extremity	0	0	1 (0.6)	1 (1.7)	2 (3.4)	0
Balance disorder	2 (1.1)	0	0	1 (1.7)	0	0
Disturbance in attention	2 (1.1)	0	0	0	0	1 (1.6)
Dizziness	6 (3.3)	2 (1.1)	0	0	3 (5.1)	2 (3.3)
Headache	2 (1.1)	1 (0.6)	5 (2.8)	0	1 (1.7)	0
Sedation	2 (1.1)	0	0	1 (1.7)	0	0
Somnolence	10 (5.5)	0	3 (1.7)	1 (1.7)	0	3 (4.9)
Day dreaming	2 (1.1)	0	0	0	0	0
Depression	2 (1.1)	0	3 (1.7)	0	0	1 (1.6)
Insomnia	0	3 (1.7)	2 (1.1)	0	0	0
Hypertension	0	2 (1.1)	0	0	1 (1.7)	0

MedDRA (Version 14.0) coding was applied.
AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; N = Number of subjects evaluable for AEs.

Dose Reductions or Temporary Discontinuations due to Adverse Events: The summary of subjects with temporary discontinuations or dose reductions due to AEs is provided in Table 37.

Table 37. Temporary Discontinuations or Dose Reductions due to Adverse Events in ≥2 Subjects Per Preferred Term

Number (%) of subjects with AE by: MedDRA (version 14.0) preferred term	Pregabalin 300 mg N=182	Pramipexole 0.25 mg N=178	Pramipexole 0.50 mg N=180	Placebo to Pregabalin 300 mg N=59	Placebo to Pramipexole 0.25 mg N=59	Placebo to Pramipexole 0.50 mg N=61
Diarrhea	1 (0.5)	1 (0.6)	1 (0.6)	0	0	1 (1.6)
Nausea	1 (0.5)	1 (0.6)	0	0	0	0
Vomiting	0	0	1 (0.6)	0	1 (1.7)	0
Gastroenteritis	0	1 (0.6)	2 (1.1)	0	0	0
Influenza	0	1 (0.6)	0	1 (1.7)	0	2 (3.3)

MedDRA (Version 14.0) coding was applied.
AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; N = Number of subjects evaluable for AEs.

Death: One subject on placebo to pregabalin 300 mg treatment died during study drug treatment due to a cerebrovascular accident. The death was not considered related to study treatment.

Laboratory Evaluations: There were no clinically meaningful differences in laboratory values among treatment groups in the median changes from Baseline to the last observation. The percentages of subjects with maximum increases or decreases in vital sign data were generally similar between treatment groups, the percentage of subjects with a maximum increase from Baseline in standing systolic blood pressure (BP) was slightly higher in the pramipexole 0.25 mg and placebo to pramipexole 0.50 mg treatment groups, and the percentage of subjects with a maximum increase from Baseline in supine diastolic BP was higher in the placebo to pregabalin 300 mg treatment group. The percentages of subjects who experienced maximum decreases from Baseline in supine and standing systolic BP and diastolic BP were lower in the placebo to pramipexole 0.50 mg treatment group, compared to the other treatment groups.

At Week 52, no significant changes in electrocardiogram were reported.

CONCLUSIONS: Pregabalin 300 mg/day demonstrated significant improvements in RLS subjects in each of the 3 co-primary endpoints: the difference of change from Baseline in the IRLS total score (compared to placebo for 12 weeks and pramipexole 0.25 and 0.5 mg/day for 12 and 52 weeks), CGI-I responder rates (compared to placebo over 12 weeks), and reduction in the rate of augmentation (compared to pramipexole 0.5 mg/day). Pregabalin 300 mg/day demonstrated lesser augmentation severity than both pramipexole 0.25 and 0.5 mg/day. Pregabalin 300 mg/day in this study population was shown to be safe, well tolerated, and consistent with the known safety profile of pregabalin.