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

PROTOCOL NO.: A0081165

PROTOCOL TITLE: Effects of Pregabalin on Sleep Maintenance in Subjects With Fibromyalgia Syndrome and Sleep Maintenance Disturbance: A Randomized Placebo-Controlled 2-Way Crossover Polysomnography Study

Study Centers: A total of 19 centers took part in the study, including 3 centers in Canada, 3 centers in Germany, and 13 centers in the United States.

Study Initiation Date and Final Completion Dates: 08 June 2009 to 03 June 2010

Phase of Development: Phase 3

Study Objectives: The primary objective was to demonstrate the effect of pregabalin compared to placebo on sleep maintenance as measured by wake after sleep onset (WASO) obtained by polysomnography (PSG) in subjects with fibromyalgia and sleep maintenance disturbance.

Secondary Objectives:

- To characterize the effect of pregabalin on other measures of sleep maintenance in subjects with fibromyalgia using PSG, including: total sleep time (TST), sleep efficiency (SE), number of awakenings after sleep onset (NAASO), wake time during sleep (WTDS), wake time after sleep (WTAS), latency to persistent sleep (LPS), and slow-wave sleep (SWS);

- To investigate the effect of pregabalin on overall sleep problem index and sleep disturbance (as measured by specific medical outcomes study – sleep scale [MOS-SS] subscales and numeric rating scale [NRS] sleep quality score);

- To characterize the effect of pregabalin on sleep maintenance as determined by subject rated assessments of subjective wake after sleep onset (sWASO) and subjective total sleep time (sTST), latency to sleep onset (LSO), and pain, as determined by NRS pain score;

- To investigate the safety and tolerability of pregabalin in subjects with fibromyalgia and sleep disturbance.

METHODS

Study Design: This was a randomized, double-blind, placebo-controlled, 2-treatment, 2-period crossover, multicenter PSG study in subjects with fibromyalgia and both subjective and objective evidence of sleep maintenance disturbance. After completing screening, all subjects entered a single-blind placebo run-in period that lasted 1 to 2 weeks, including PSG at baseline. Subjects who continued to meet inclusion/exclusion criteria were randomized and entered 2 double-blind treatment periods, each consisting of 2 phases:

1. Dose-adjustment of study treatment (up to Day 14); and

2. Maintenance of treatment (to Day 29).

There was a taper period (3 days) after each double-blind crossover period, and a 11-day washout period between the crossover periods during which subjects received single-blind placebo. The schedule of activities is presented in Table 1.

Table 1. Schedule of Activities

Study Phase	Screen[a]	Baseline/Single Blind Period		Double-Blind Crossover Period 1						Double-Blind Crossover Period 2					
Clinic Visit Number	V1[a]	V2	V3	V4[b]	TC[c]	TC[c]	TC[c]	TC[d]	V5[e]	V6	TC	TC[c]	TC[c]	TC[d]	V7/ET[f]
Study Week	-4 to -2	-2 to -1	-1	1		2	3-4		5	7		8	9-10		11
Visit Type	Screen	Placebo run-in	BL PSG	Rand	Dose Adjust		Dose Maintenance		PSG/ Clinic	Dose Adjust			Dose Maintenance		PSG/Clinic/ Final Visit
Day	-28 to -15	-14 to -7	-7 to -6	1	4	8	15	22	28/29, 30	1 (44)	4 (47)	8 (51)	15 (58)	22 (65)	28/29, 30 (71/72, 73)
Observation/Procedure															
Informed consent	X														
Inclusion/exclusion	X	X	X	X											
Medical history/demography	X														
Physical examination (includes neurological exam)	X														
Tender point count	X														
Height, weight, and vital signs[g]	X			X					X						X
12-lead ECG	X														
Clinical laboratory tests	X														
Urine drug screen	X	X													
Breathalyzer test[h]			X[h]						X[h]						X[h]
Pregnancy test[i]	X[i]			X											X
HADS	X			X											
MINI	X														
Single blind placebo medication dispensing/dosing/accountability		X		(X)[e]											
Randomization				X											
Double blind study medication[c] dispensing/ dosing/accountability				X					X[e]	X					X[e]
Taper/washout medication[e]									X[e]	X[e]					X[e, j]
Assessments (Efficacy)															
PSG (2 nights/study visit)[h]			X						X						X
Daily IVRS diary (NRS pain, tiredness; SSQ)		X	X	X	X	X	X		X	X	X	X	X	X	X
MOS-SS		X		X					X	X					X
Actigraphy armband[d]		X[d]		X[d]				X[d]	X[d]	X[d]				X[d]	X[d]
PHQ-8	X														
STS	X			X					X	X					X

Table 1. Schedule of Activities

Study Phase	Screen[a]	Baseline/Single Blind Period		Double-Blind Crossover Period 1						Double-Blind Crossover Period 2					
Clinic Visit Number	V1[a]	V2	V3	V4[b]	TC[c]	TC[c]	TC[c]	TC[d]	V5[e]	V6	TC	TC[c]	TC[c]	TC[d]	V7/ET[f]
Study Week	-4 to -2	-2 to -1	-1	1		2	3-4		5	7		8	9-10		11
Visit Type	Screen	Placebo run-in	BL PSG	Rand	Dose Adjust		Dose Maintenance		PSG/ Clinic	Dose Adjust			Dose Maintenance		PSG/Clinic/ Final Visit
Day	-28 to -15	-14 to -7	-7 to -6	1	4	8	15	22	28/29, 30	1 (44)	4 (47)	8 (51)	15 (58)	22 (65)	28/29, 30 (71/72, 73)
Observation/Procedure															
Adverse events		X	X	X	X	X	X	X	X	X	X	X	X	X	X[j]
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

BID = twice daily; BL = baseline; ECG = electrocardiogram; ET = early termination; HADS = hospital anxiety and depression scale; IVRS = interactive voice response system; MINI = mini international neuropsychiatric interview; MOS-SS = medical outcome study-sleep scale; NRS = numeric rating scale; PSG = polysomnography; PHQ-8 = patient health questionnaire; Rand = randomization; SSQ = subjective sleep questionnaire; STS = suicidality tracking scale; TC = telephone contact; V = visit.

a. Visit 1 may have occurred from 4 weeks to 1 week prior to Visit 2, according to need for washout, and time required for Screening procedures. Repeat of certain measures may be required if the interval was exceeded, on a case by case basis.
b. Randomization (Visit 4) was to occur upon verification of all eligibility including PSG. It may have occurred up to 7 days after PSG (Visit 3).
c. Subject was dispensed 3 bottles at Visit 4 and 6, with instructions for BID dosing in the AM upon awakening, and in the PM 1 hour before bedtime. Telephone contacts were to be made at Day 4, Day 8, Day 15 in each phase to verify compliance, to titrate to the next bottle, and for any interim upward or downward adjustments as deemed necessary by the Investigator. The contact and any resulting dose adjustments were documented.
d. Subjects were given Actigraphy armband and instructed as to its use at Visit 2, and asked to wear the armband until Visit 3 PSG (or Screen Failure). Randomized subjects were given the armband at Visits 4 and 6, and were instructed during the Day 22 Telephone Contact of each crossover period to begin wearing the armband from that day until their return for PSG at Day 28. Armband was to be returned for data download at Clinic Visits 3, 5, and 7/ET.
e. Used and unused bottles of study medication (single- and double-blind) were returned to the site at all clinic visits and accountability performed. After Visit 5, subjects were dispensed 2 bottles of medications for 2 weeks taper/wash-out period until Visit 6. After Visit 7, taper medication was returned to the study center.
f. In the event of ET, Visit 7 procedures were to be performed. PSG was not to be performed if subject had not taken study medication for more than 2 days.
g. Height was measured at screening only.
h. Breathalyzer test was to be given to subject prior to each night of PSG.
i. Serum pregnancy test was at Screening only; all other pregnancy tests were urine pregnancy.
j. At Visit 7, subject was instructed regarding drug return. An optional follow-up visit or telephone call may have been scheduled for after the taper at the Investigator's discretion to allow for follow-up of any outstanding safety issues.

Number of Subjects (Planned and Analyzed): The study planned to enroll approximately 100 subjects. A total of 557 subjects were screened; 119 were randomized and treated: 15 in Canada, 20 in Germany and 84 in the United States. One hundred and two (85.7%) subjects completed the study and 17 (14.3%) withdrew prematurely.

Fifty-two (86.7%) of the 60 subjects randomized and treated in the placebo→pregabalin sequence and 50 (84.7%) of the 59 subjects randomized and treated in the pregabalin→placebo sequence completed the study.

Diagnosis and Main Criteria for Inclusion: Subjects included in the study must have met diagnostic criteria for fibromyalgia; must have reported difficulty in maintaining sleep at least 3 times per week, and must have met Research Diagnostic Criteria (RDC) for insomnia disorder.

Study Treatment: Study medication was supplied by the Sponsor as blinded capsules containing 75, 150, or 225 mg pregabalin and matching placebo. Duration of study treatment was approximately 60 days. The study dosing schedule is presented in Table 2.

Table 2. Dosing Schedule (BID dosing)[a]

	Screening	Dose Adjustment			Dose Maintenance[b]	Taper/ Washout	
	Days -15 to 0	Day 1-3	Day 4-7[c]	Day 8-14[d]	Days 15-29	Taper Days 1-3	Taper Days 4-14[e]
Placebo	Placebo	Bottle A	Bottle B	Bottle C	Bottle C	Bottle D	Bottle E[f]
150 mg/day	Placebo	Bottle A	Bottle A[c]	Bottle A	Bottle A	Bottle D	Bottle E
300 mg/day	Placebo	Bottle A	Bottle B	Bottle B[d]	Bottle B	Bottle D	Bottle E
450 mg/day	Placebo	Bottle A	Bottle B	Bottle C	Bottle C	Bottle D	Bottle E

BID = twice daily; PSG = polysomnogram.

a. Subjects were instructed to take 1 capsule in the morning upon awakening, and in the evening approximately 1 hour before bedtime.
b. No dose adjustments could have been made after Day 15. Upward titration must have been done no later than Day 13 to allow for reduction if necessary. Maintenance dose was to be continued until dispensing of taper medication after PSG.
c. All subjects were to be titrated to Bottle B (150 mg capsules; BID=300 mg/day or placebo) on Day 4. Subjects unable to tolerate 300 mg/day (Bottle B) were allowed to continue in the study on Bottle A (75 mg capsules; BID=150 mg/day or placebo). On Day 4, the dose was increased to 150 mg BID (300 mg/day) or placebo (Bottle B) except in cases of intolerability. Subjects unable to tolerate 300 mg/day were allowed to continue on 150 mg/day (Bottle A) for the duration of the study.
d. Beginning Day 8, subjects who have tolerated 300 mg/day (Bottle B) for a minimum of 4 days were to be titrated to Bottle C (225 mg capsules; BID=450 mg/day or placebo). This upward titration can occur until Day 13. Subjects unable to tolerate 450 mg/day could be reduced back to 300 mg/day (Bottle B) no later than Day 15.
e. Subjects were dispensed 2 bottles during the washout period between crossover periods. At the end of crossover period 2 they were dispensed only Bottle D (75 mg capsules; BID=150 mg/day or placebo).
f. Bottle E = placebo for washout.

Efficacy Endpoints: The primary efficacy endpoint was the mean WASO as determined by PSG assessment.

Secondary endpoints were:

- PSG endpoints: NAASO, TST, SE
- MOS-SS subscales: Sleep Disturbance, Snoring, Awaken with Shortness of Breath or with Headache, Quantity of Sleep, Sleep Adequacy, Somnolence, Overall Sleep Problem Index, and Optimal Sleep
- Subjective Total Sleep Time (sTST) from daily Subjective Sleep Questionnaire (SSQ) obtained using IVRS or eDiary
- All serious adverse events, all treatment-emergent adverse events

Safety Evaluations: Safety and tolerability were measured by adverse event (AE) reporting, vital sign measurements, weight measurements, electrocardiogram (ECG), physical examination, laboratory evaluations, and the administration of the Sheehan Suicidality Tracking Scale (STS).

Statistical Methods: Intent to treat (ITT) Population: All subjects who were randomized, treated (ie received at least 1 dose of study medication) and had at least 1 efficacy evaluation. Safety Population: All randomized subjects who received at least 1 dose of study medication. Per Protocol Population (PPA): All randomized subjects who received the study medication at a dose of 300 or 450 mg/day and completed the study without any major protocol violations. The primary analysis was conducted using the PPA population; the ITT population was used for secondary analyses.

The primary endpoint (WASO as determined by PSG) was analyzed using a linear mixed effects model including sequence, period, and treatment as fixed factors, and subject within sequence and within-subject error as random factors. The point estimate for mean treatment difference (pregabalin – placebo) and 95% confidence intervals (CIs) for the true mean treatment difference were reported. Descriptive statistics were also reported for the primary efficacy endpoint by visit and treatment group. For the continuous endpoints such as PSG endpoints TST, SE, number of awakenings after sleep onset: wake period of at least 1 epoch duration (NAASO1), number of awakenings after sleep onset: wake period of at least 2 epochs duration (NAASO2), WTDS, WTAS, LPS, SWS, and subjective endpoints sWASO, sTST, LSO, NRS pain score, NRS sleep quality score, and MOS-SS subscales, the same statistical analysis methods as specified for the primary efficacy endpoint were used. For the statistical analysis of the MOS-SS score, where the baseline measurement was taken in each period, the baseline measurement for each period was included as a covariate in the statistical model being used. The component 'Optimal Sleep' was analyzed using Cochran-Mantel-Haenszel (CMH) general association method.

Weekly averages of the secondary endpoints from the daily IVRS diary assessments from the dose maintenance period from each crossover period were used in the statistical analysis, and descriptive statistics were provided.

Safety evaluations were summarized using the Sponsor's safety reporting standards.

RESULTS

Subject Disposition and Demography: Four subjects were randomized twice, and treated simultaneously for at least 2 days at 2 study centers. Data from the second randomization of these subjects were excluded from the ITT population. Table 3 presents subject evaluation groups and disposition.

Table 3. Subject Evaluation Groups and Disposition

Number (%) of Subjects	Placebo	Pregabalin	All Subjects
Entered screening	-	-	557
Withdrawn during screening	-	-	438 (78.6[a])
Randomized and treated[b]	111 (93.3[c])	112 (94.1[c])	119 (21.4[a])
Completed	103[d] (91.1[e])	103[d] (91.9[e])	102 (85.7[c])
Discontinued	8 (7.2[e])	9 (8.0[e])	17 (14.3[c])
Adverse event	1 (0.9[e])	2 (1.8[e])	3 (2.5[c])
Protocol violation	3 (2.7[e])	7 (6.3[e])	10 (8.4[c])
Subject defaulted[f]	4 (3.6[e])	0	4 (3.4[c])
Analyzed for efficacy			
ITT	109 (98.2[e])	108 (96.4[e])	115 (96.6[c])
Reasons not included in ITT	-	-	4 (3.4[c])
Subject was randomized and treated more than once[g]	-	-	4 (3.4[c])
PPA	83 (74.8[e])	83 (74.1[e])	83 (69.7[c])
Reasons not included in PPA[h]	-	-	36 (30.3[c])
Did not complete study	-	-	17 (14.3[c])
Did not reach required maintenance dose[i] in Period 1	-	-	3 (2.5[c])
Did not reach required maintenance dose[i] in Period 2	-	-	4 (3.4[c])
Subject was randomized and treated more than once	-	-	13 (10.9[c])
Dosing compliance outside 80-120% in Period 1	-	-	3 (2.5[c])
Dosing compliance outside 80-120% in Period 2	-	-	6 (5.0[c])
Analyzed for safety	-	-	
Adverse events	111 (100.0[e])	112 (100.0[e])	119 (100.0[c])

ITT = intent to treat; PPA = per protocol analysis.

a. Denominator was number of subjects screened overall.
b. One subject received only pregabalin and was not crossed over to placebo in Period 2 as expected per protocol.
c. Denominator was number of subjects randomized overall.
d. One subject in each sequence completed only Period 1 but not Period 2.
e. Denominator was number of subjects randomized and treated in that arm.
f. Subject defaulted included subjects who withdrew consent and subjects lost to follow-up.
g. Data from the first time the subject was randomized and treated were not excluded from the ITT population.
h. Subjects may have been be represented in more than 1 reason, so total number of subjects listed would not have matched total number of subjects excluded from PPA.
i. Before the study was unblinded, a subject was determined to have reached the required maintenance dose if she/he was documented as receiving Bottle B or Bottle C during the maintenance phase.

The mean duration of time since diagnosis with fibromyalgia was 4.2 years (range 0 to 26.3 years). Sixty-six (55.5%) subjects had insomnia. Demography characteristics are summarized in Table 4.

Table 4. Demographic Characteristics

	Male N=16	Female N=103	All Subjects N=119
Age (years) n (%)			
18-44	9 (56.3)	36 (35.0)	45 (37.8)
45-64	7 (43.8)	62 (60.2)	69 (58.0)
≥65	0	5 (4.9)	5 (4.2)
Mean (SD)	45.7 (7.1)	48.8 (10.3)	48.4 (9.9)
Range	33–55	27–77	27–77
Race n (%)			
White	15 (93.8)	89 (86.4)	104 (87.4)
Black	1 (6.3)	7 (6.8)	8 (6.7)
Asian	0	2 (1.9)	2 (1.7)
Other	0	5 (4.9)	5 (4.2)
Weight (kg)			
Mean (SD)	87.6 (9.8)	73.7 (18.2)	75.6 (17.9)
Range	68.9–100.4	44.4–174.9	44.4–174.9
Height (cm)			
Mean (SD)	178.1 (7.3)	161.7 (8.0)	163.9 (9.7)
Range	163.0–190.5	142.0–178.0	142.0–190.5

SD = standard deviation; N = number of subjects; n = number of subjects per variable.

Efficacy Results: Treatment with pregabalin resulted in statistically significantly reduced least squares (LS) mean WASO compared to treatment with placebo (Table 5).

Table 5. Analysis of Primary Endpoint: WASO (Minutes) From PSG (PPA)

Statistic	Placebo	Pregabalin
N	83	83
LS Mean (SE)	70.69 (3.78)	51.54 (3.78)
LS Mean difference from placebo	-19.15	
95% CI for LS Mean difference from placebo	(-26.69, -11.61)	
p-value	<0.0001	

p-value based on a linear mixed effects model including sequence, period, and treatment as fixed factors, and subject within sequence and within-subject error as random factors.
CI = confidence interval; LS mean = least squares mean; N = number of subjects; PSG = polysomnography; PPA = per protocol analysis; SE = standard error; WASO = wake after sleep onset.

Sensitivity analysis of WASO for the ITT population confirmed the results of the primary analysis.

A summary of secondary PSG assessments related to sleep induction and maintenance are presented in Table 6.

Table 6. Analysis of Secondary PSG Assessments for Sleep Induction and Maintenance (ITT)

PSG Parameter	Statistic	Placebo N=109	Pregabalin N=108
TST[a] (minutes)	LS Mean (SE)	370.6 (4.65)	396.2 (4.69)
	LS Mean difference from placebo	25.54	
	95% CI for LS Mean difference from placebo	(17.48, 33.61)	
	p-value	<0.0001	
Sleep efficiency[a] (percent)	LS Mean (SE)	77.21 (0.97)	82.64 (0.98)
	LS Mean difference from placebo	5.42	
	95% CI for LS Mean difference from placebo	(3.74, 7.11)	
	p-value	<0.0001	
NAASO1[b] (number)	LS Mean (SE)	26.92 (1.00)	24.51 (1.00)
	LS Mean difference from placebo	-2.41	
	95% CI for LS Mean difference from placebo	(-4.31, -0.51)	
	p-value	0.0135	
NAASO2[b] (number)	LS Mean (SE)	10.16 (0.44)	8.63 (0.45)
	LS Mean difference from placebo	-1.53	
	95% CI for LS Mean difference from placebo	(-2.41, -0.66)	
	p-value	0.0008	
WTDS[b] (minutes)	LS Mean (SE)	63.38 (2.90)	45.83 (2.93)
	LS Mean difference from placebo	-17.54	
	95% CI for LS Mean difference from placebo	(-23.29, -11.80)	
	p-value	<0.0001	
WTAS[b] (minutes)	LS Mean (SE)	9.19 (1.55)	7.38 (1.57)
	LS Mean difference from placebo	-1.81	
	95% CI for LS Mean difference from placebo	(-5.92, 2.30)	
	p-value	0.3841	
LPS[b] (minutes)	LS Mean (SE)	41.63 (3.70)	34.45 (3.74)
	LS Mean difference from placebo	-7.18	
	95% CI for LS Mean difference from placebo	(-14.18, -0.17)	
	p-value	0.0447	
SWS[a,c] (as % of TST)	LS Mean (SE)	15.04 (1.01)	17.18 (1.01)
	LS Mean difference from placebo	2.14	
	95% CI for LS Mean difference from placebo	(0.78, 3.50)	
	p-value	0.0024	

p-value based on a linear mixed effects model including sequence, period, and treatment as fixed factors, and subject within sequence and within-subject error as random factors.
CI = confidence interval; ITT = intent to treat; LPS = latency to persistent sleep; LS Mean = least squares mean; N = number of subjects; NAASO1 = number of awakenings after sleep onset: wake period of at least 1 epoch duration; NAASO2 = number of awakenings after sleep onset: wake period of at least 2 epochs' duration; PSG = polysomnography; SE = standard error; SWS = slow wave sleep; TST = total sleep time; WTAS = wake time after sleep; WTDS = wake time during sleep.

a. Higher LS mean values and positive LS mean differences indicate improved sleep.
b. Lower LS mean values and negative LS mean differences indicate improved sleep.
c. SWS was defined as Stage 3+4 sleep.

Treatment with pregabalin resulted in statistically significantly reduced LS mean WASO for hours 3 through 7 ($p<0.04$) compared to treatment with placebo. Treatment with pregabalin resulted in statistically significantly reduced LS mean WASO ($p<0.02$) for all but the first quarter of the night compared to treatment with placebo. A summary of WASO by quarter of the night from the PSG for the ITT population is presented in Table 7.

Table 7. Analysis of Secondary PSG Assessments WASO (Minutes) by Quarter of the Night (ITT)

Quarter of the Night	Statistic	Placebo N=109	Pregabalin N=108
First quarter (Hours 1-2)	LS Mean (SE)	7.23 (0.63)	5.98 (0.64)
	LS Mean difference from placebo	-1.25	
	95% CI for LS Mean difference from placebo	(-2.79, 0.29)	
	p-value	0.1106	
Second quarter (Hours 3-4)	LS Mean (SE)	16.04 (1.05)	10.04 (1.06)
	LS Mean difference from placebo	-6.00	
	95% CI for LS Mean difference from placebo	(-8.49, -3.51)	
	p-value	<0.0001	
Third quarter (Hours 5-6)	LS Mean (SE)	21.73 (1.58)	14.90 (1.60)
	LS Mean difference from placebo	-6.83	
	95% CI for LS Mean difference from placebo	(-10.53, -3.13)	
	p-value	0.0004	
Fourth quarter (Hours 7-8)	LS Mean (SE)	28.04 (1.98)	22.60 (2.00)
	LS Mean difference from placebo	-5.44	
	95% CI for LS Mean difference from placebo	(-10.00, -0.88)	
	p-value	0.0199	

p-value based on a linear mixed effects model including sequence, period, and treatment as fixed factors, and subject within sequence and within-subject error as random factors.
CI = confidence interval; ITT = intent to treat; LS Mean = least squares mean; N = number of subjects; PSG = polysomnography; SE = standard error; WASO = wake after sleep onset.

A summary of WASO by hour from the PSG for the ITT population is presented in Table 8.

Table 8. Analysis of Secondary PSG Assessments WASO (Minutes) by Hour (ITT)

Hour	Statistic	Placebo N=109	Pregabalin N=108
Hour 1	LS Mean (SE)	1.96 (0.27)	1.62 (0.28)
	LS Mean difference from placebo	-0.34	
	95% CI for LS Mean difference from placebo	(-1.07, 0.39)	
	p-value	0.3613	
Hour 2	LS Mean (SE)	5.66 (0.52)	4.56 (0.53)
	LS Mean difference from placebo	-1.10	
	95% CI for LS Mean difference from placebo	(-2.29, 0.09)	
	p-value	0.0686	
Hour 3	LS Mean (SE)	7.09 (0.54)	4.65 (0.55)
	LS Mean difference from placebo	-2.44	
	95% CI for LS Mean difference from placebo	(-3.85, -1.03)	
	p-value	0.0009	
Hour 4	LS Mean (SE)	8.95 (0.75)	5.43 (0.75)
	LS Mean difference from placebo	-3.52	
	95% CI for LS Mean difference from placebo	(-5.33, -1.71)	
	p-value	0.0002	
Hour 5	LS Mean (SE)	10.55 (0.90)	7.54 (0.90)
	LS Mean difference from placebo	-3.01	
	95% CI for LS Mean difference from placebo	(-5.16, -0.86)	
	p-value	0.0065	
Hour 6	LS Mean (SE)	11.26 (0.94)	7.38 (0.95)
	LS Mean difference from placebo	-3.89	
	95% CI for LS Mean difference from placebo	(-6.36, -1.41)	
	p-value	0.0024	
Hour 7	LS Mean (SE)	10.96 (0.91)	8.38 (0.92)
	LS Mean difference from placebo	-2.59	
	95% CI for LS Mean difference from placebo	(-5.01, -0.16)	
	p-value	0.0366	
Hour 8	LS Mean (SE)	17.08 (1.34)	14.23 (1.35)
	LS Mean difference from placebo	-2.85	
	95% CI for LS Mean difference from placebo	(-5.82, 0.11)	
	p-value	0.0593	

p-value based on a linear mixed effects model including sequence, period, and treatment as fixed factors, and subject within sequence and within-subject error as random factors.
CI = confidence interval; ITT = intent to treat; LS Mean = least squares mean; N = number of subjects; PSG = polysomnography; SE = standard error; WASO = wake after sleep onset.

The analysis of SSQ parameter is presented in Table 9.

Table 9. Analysis of SSQ Parameter at Weeks 1, 2, 3, and 4 (ITT)

Timepoint / Statistic	sWASO		sTST		LSO	
	Placebo N=109	Pregabalin N=108	Placebo N=109	Pregabalin N=108	Placebo N=109	Pregabalin N=108
Week 1						
LS Mean (SE)	80.86 (3.71)	62.59 (3.73)	336.8 (5.40)	361.7 (5.41)	51.23 (2.61)	43.56 (2.61)
LS Mean difference from placebo	-18.27		24.82		-7.66	
95% CI for LS Mean difference from placebo	(-27.02, -9.52)		(13.25, 36.40)		(-11.44, -3.89)	
p-value	<0.0001		<0.0001		0.0001	
Week 2						
LS Mean (SE)	75.48 (3.91)	59.43 (3.92)	341.9 (5.76)	371.3 (5.77)	49.94 (2.92)	42.27 (2.92)
LS Mean difference from placebo	-16.06		29.40		-7.67	
95% CI for LS Mean difference from placebo	(-24.24, -7.87)		(18.59, 40.21)		(-13.27, -2.07)	
p-value	0.0002		<0.0001		0.0077	
Week 3						
LS Mean (SE)	74.97 (4.75)	61.73 (4.76)	344.1 (5.73)	370.9 (5.74)	48.92 (4.01)	43.24 (4.02)
LS Mean difference from placebo	-13.23		26.79		-5.68	
95% CI for LS Mean difference from placebo	(-23.01, -3.46)		(15.37, 38.21)		(-14.81, 3.44)	
p-value	0.0085		<0.0001		0.2196	
Week 4 (LOCF)						
LS Mean (SE)	69.65 (4.20)	59.40 (4.21)	352.5 (5.60)	377.9 (5.61)	46.70 (2.68)	40.51 (2.68)
LS Mean difference from placebo	-10.25		25.44		-6.18	
95% CI for LS Mean difference from placebo	(-18.01, -2.48)		(15.03, 35.86)		(-10.73, -1.64)	
p-value	0.0102		<0.0001		0.0081	

Week values were calculated as the average of the daily diary scores.
p-value based on a linear mixed effects model including sequence, period, and treatment as fixed factors, and subject within sequence and within-subject error as random factors.
CI = confidence interval; ITT = intent to treat; LOCF = last observation carried forward; LS Mean = least squares mean; LSO = latency to sleep onset; N = number of subjects; SE = standard error; SSQ = subjective sleep questionnaire; sTST = subjective total sleep time; sWASO = subjective wake after sleep onset.

For all 4 weeks of treatment, treatment with pregabalin resulted in statistically significantly improved LS mean subjective sleep efficiency compared to treatment with placebo ($p<0.0001$).

For all 4 weeks of treatment, treatment with pregabalin resulted in statistically significantly greater (better) LS mean NRS sleep quality scores compared to treatment with placebo ($p<0.0001$).

Scores at the end of Period 1 were compared to the scores at the start of Period 1, and scores at the end of Period 2 were compared to the scores at the start of Period 2. Subscales for which treatment with pregabalin resulted in statistically significant improvements compared to treatment with placebo were Sleep Disturbance, Quantity of Sleep, and Sleep Problems Index II (in Period 2) and Sleep Adequacy (in both periods). The summary of change from baseline for the MOS-SS subscales is presented in Table 10.

Table 10. Analysis of Change From Period Baselines in MOS-SS Subscales (ITT)

MOS-SS Subscale	Pd	Statistic	Placebo N=109	Pregabalin N=108
Sleep disturbance[a]	1	N	59	56
		LS Mean change from period baseline (SE)	-19.0 (2.98)	-27.1 (3.06)
		LS Mean change difference from placebo	-8.13	
		95% CI for LS Mean change difference from placebo	(-16.59, 0.32)	
		p-value	0.0591	
	2	N	50	52
		LS Mean change from period baseline (SE)	-2.23 (3.10)	-21.0 (3.04)
		LS Mean change difference from placebo	-18.81	
		95% CI for LS Mean change difference from placebo	(-27.43, -10.20)	
		p-value	<0.0001	
Sleep adequacy[b]	1	N	59	56
		LS Mean change from period baseline (SE)	15.82 (3.53)	28.51 (3.62)
		LS Mean change difference from placebo	12.69	
		95% CI for LS Mean change difference from placebo	(2.67, 22.71)	
		p-value	0.0136	
	2	N	50	52
		LS Mean change from period baseline (SE)	-0.95 (3.75)	16.30 (3.68)
		LS Mean change difference from placebo	17.25	
		95% CI for LS Mean change difference from placebo	(6.79, 27.72)	
		p-value	0.0015	
Quantity of sleep[c] (Hours)	1	N	59	56
		LS Mean change from period baseline (SE)	0.53 (0.15)	0.89 (0.16)
		LS Mean change difference from placebo	0.37	
		95% CI for LS Mean change difference from placebo	(-0.07, 0.81)	
		p-value	0.0996	
	2	N	50	52
		LS Mean change from period baseline (SE)	0.14 (0.12)	0.69 (0.12)
		LS Mean change difference from placebo	0.55	
		95% CI for LS Mean change difference from placebo	(0.21, 0.88)	
		p-value	0.0015	
Snoring[d]	1	N	59	56
		LS Mean change from period baseline (SE)	-4.48 (1.98)	-0.64 (2.03)
		LS Mean change difference from placebo	3.84	
		95% CI for LS Mean change difference from placebo	(-1.81, 9.48)	
		p-value	0.1807	
	2	N	50	52
		LS Mean change from period baseline (SE)	0.97 (2.11)	-0.54 (2.07)
		LS Mean change difference from placebo	-1.51	
		95% CI for LS Mean change difference from placebo	(-7.41, 4.39)	
		p-value	0.6126	
Somnolence[e]	1	N	59	56
		LS Mean change from period baseline (SE)	-10.8 (2.03)	-8.01 (2.08)
		LS Mean change difference from placebo	2.81	
		95% CI for LS Mean change difference from placebo	(-2.95, 8.58)	
		p-value	0.3356	
	2	N	50	52
		LS Mean change from period baseline (SE)	-0.79 (2.40)	-1.93 (2.36)
		LS Mean change difference from placebo	-1.13	
		95% CI for LS Mean change difference from placebo	(-7.81, 5.55)	
		p-value	0.7372	
Awakening with short of	1	N	59	56
		LS Mean change from period baseline (SE)	-7.75 (2.37)	-7.19 (2.43)

Table 10. Analysis of Change From Period Baselines in MOS-SS Subscales (ITT)

MOS-SS Subscale	Pd	Statistic	Placebo N=109	Pregabalin N=108
breath or with headache[f]		LS Mean change difference from placebo	0.57	
		95% CI for LS Mean change difference from placebo	(-6.17, 7.30)	
		p-value	0.8679	
	2	N	50	52
		LS Mean change from period baseline (SE)	-2.47 (2.79)	-7.24 (2.73)
		LS Mean change difference from placebo	-4.78	
		95% CI for LS Mean change difference from placebo	(-12.53, 2.97)	
		p-value	0.2241	
Sleep problems index II[g]	1	N	59	56
		LS Mean change from period baseline (SE)	-16.4 (2.37)	-21.9 (2.43)
		LS Mean change difference from placebo	-5.47	
		95% CI for LS Mean change difference from placebo	(-12.20, 1.26)	
		p-value	0.1101	
	2	N	50	52
		LS Mean change from period baseline (SE)	-0.98 (2.51)	-14.4 (2.46)
		LS Mean change difference from placebo	-13.39	
		95% CI for LS Mean change difference from placebo	(-20.36, -6.42)	
		p-value	0.0002	

Baseline MOS-SS for Period 1 = Visit 4, Baseline MOS-SS for Period 2 = Visit 6.
p-value based on a linear mixed effects model including sequence, period, and treatment as fixed factors, and subject within sequence and within-subject error as random factors.
CI = confidence interval; ITT = intent to treat; LS Mean = least squares mean; MOS-SS = medical outcomes study-sleep scale; N = number of subjects; Pd = period; SE = standard error.

a. Range = 0 to 100; higher scores indicate greater sleep disturbance. Negative changes indicate improvement.
b. Range = 0 to 100; higher scores indicate greater sleep adequacy. Negative changes indicate improvement.
c. Range = 0 to 24; higher scores indicate greater quantity of sleep. Positive changes indicate improvement.
d. Range = 0 to 100; higher scores indicate greater snoring. Negative changes indicate improvement.
e. Range = 0 to 100; higher scores indicate greater somnolence. Negative changes indicate improvement.
f. Range = 0 to 100; higher scores indicate greater shortness of breath or headache. Negative changes indicate improvement.
g. 9-item index. Range = 0 to 100; higher scores indicate greater sleep problems. Negative changes indicate improvement.

The summary of MOS-SS optimal sleep subscale is presented in Table 11.

Table 11. Analysis of MOS-SS Optimal Sleep Scale (ITT)

Crossover Period	Visit	Treatment	N	Non-Optimal Sleep n (%)	Optimal Sleep n (%)	p-Value
Period 1						
Baseline	Visit 4	Placebo	59	57 (96.6)	2 (3.4)	
		Pregabalin	56	55 (98.2)	1 (1.8)	
End of Pd	Visit 5	Placebo	59	53 (89.8)	6 (10.2)	
		Pregabalin	56	42 (75.0)	14 (25.0)	0.0368
Period 2						
Baseline	Visit 6	Placebo	50	40 (80.0)	10 (20.0)	
		Pregabalin	52	42 (80.8)	10 (19.2)	
End of Pd	Visit 7	Placebo	50	42 (84.0)	8 (16.0)	
		Pregabalin	52	28 (53.8)	24 (46.2)	0.0011

Analyzed using Cochran-Mantel-Haenszel (CMH) general association method.
ITT = intent to treat; MOS-SS = medical outcome study-sleep scale; N = number of subjects with data; n = number of subjects in category; Pd = period.

The analysis of NRS sleep quality score is presented in Table 12.

Table 12. Analysis of NRS Sleep Quality Score (ITT, LOCF)

Timepoint / Statistic	Placebo N=109		Pregabalin N=108
Week 1			
LS Mean (SE)	4.79 (0.16)		5.70 (0.17)
LS Mean difference from placebo		0.91	
95% CI for LS Mean difference from placebo		(0.58, 1.24)	
p-value		<0.0001	
Week 2			
LS Mean (SE)	4.95 (0.18)		6.09 (0.18)
LS Mean difference from placebo		1.14	
95% CI for LS Mean difference from placebo		(0.76, 1.53)	
p-value		<0.0001	
Week 3			
LS Mean (SE)	5.09 (0.17)		5.96 (0.17)
LS Mean difference from placebo		0.87	
95% CI for LS Mean difference from placebo		(0.46, 1.28)	
p-value		<0.0001	
Week 4			
LS Mean (SE)	5.17 (0.17)		6.06 (0.17)
LS Mean difference from placebo		0.89	
95% CI for LS Mean difference from placebo		(0.51, 1.26)	
p-value		<0.0001	

Week values were calculated as the average of the daily diary scores.
p-value based on a linear mixed effects model including sequence, period, and treatment as fixed factors, and subject within sequence and within-subject error as random factors.
CI = confidence interval; ITT = intent to treat; LOCF = last observation carried forward; LS Mean = least squares mean; N = number of subjects; NRS = numeric rating scale; SE = standard error.

For all 4 weeks of treatment, treatment with pregabalin resulted in statistically significantly lower (improved) LS mean pain scores compared to treatment with placebo. The analysis of NRS pain score is presented in Table 13.

Table 13. Analysis of NRS Pain Score (ITT, LOCF)

Timepoint / Statistic	Placebo N=109		Pregabalin N=108
Week 1			
LS Mean (SE)	6.12 (0.18)		5.42 (0.18)
LS Mean difference from placebo		-0.70	
95% CI for LS Mean difference from placebo		(-1.02, -0.37)	
p-value		<0.0001	
Week 2			
LS Mean (SE)	5.81 (0.18)		5.10 (0.18)
LS Mean difference from placebo		-0.71	
95% CI for LS Mean difference from placebo		(-1.06, -0.36)	
p-value		0.0001	
Week 3			
LS Mean (SE)	5.73 (0.19)		5.14 (0.19)
LS Mean difference from placebo		-0.59	
95% CI for LS Mean difference from placebo		(-0.95, -0.24)	
p-value		0.0014	
Week 4			
LS Mean (SE)	5.44 (0.20)		4.92 (0.20)
LS Mean difference from placebo		-0.52	
95% CI for LS Mean difference from placebo		(-0.90, -0.14)	
p-value		0.0084	

Week values were calculated as the average of the daily diary scores.
p-value based on a linear mixed effects model including sequence, period, and treatment as fixed factors, and subject within sequence and within-subject error as random factors.
CI = confidence interval; ITT = intent to treat; LOCF = last observation carried forward; LS Mean = least squares mean; N = number of subjects; NRS = numeric rating scale; SE = standard error.

Safety Results: An overview of treatment-emergent AEs is presented in Table 14.

Table 14. Overview of Treatment-Emergent Adverse Events

Number (%) of Subjects	Placebo N=111	Pregabalin N=112
All Causality		
Number of adverse events	55	174
Subjects with:		
Adverse events	33 (29.7)	73 (65.2)
SAEs	0	0
Severe adverse events	1 (0.9)	0
Discontinuations due to adverse events	1 (0.9)	2 (1.8)
Dose reductions/temporary discontinuations due to adverse events	10 (9.0)	28 (25.0)
Treatment-Related		
Number of adverse events	37	140
Subjects with:		
Adverse events	23 (20.7)	64 (57.1)
SAEs	0	0
Severe adverse events	1 (0.9)	0
Discontinuations due to adverse events	1 (0.9)	2 (1.8)
Dose reductions/temporary discontinuations due to adverse events	10 (9.0)	28 (25.0)

N = number of subjects; SAE = serious adverse events.

A summary of treatment-emergent AEs occurring in at least 5% of subjects during either treatment is presented in Table 15.

Table 15. Summary of Treatment-Emergent Adverse Events Occurring in at Least 5% of Subjects (All Causalities)

Adverse Event Number (%) of Subjects	Placebo N=111	Pregabalin N=112
Dizziness	11 (9.9)	34 (30.4)
Somnolence	5 (4.5)	23 (20.5)
Headache	9 (8.1)	10 (8.9)
Nausea	3 (2.7)	8 (7.1)

Events listed were reported in at least 5% of subjects in either treatment group and are sorted by decreasing frequency in the pregabalin treatment group.
MedDRA (version 13.0) coding used.
MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects.

Treatment-emergent AEs considered related to treatment by the Investigator in at least 5% of subjects during either treatment are summarized in Table 16.

Table 16. Summary of Treatment-Emergent Treatment-Related Adverse Events Occurring in at Least 5% of Subjects

Adverse Event Number (%) of Subjects	Placebo N=111	Pregabalin N=112
Dizziness	11 (9.9)	32 (28.6)
Somnolence	5 (4.5)	23 (20.5)
Headache	7 (6.3)	8 (7.1)
Nausea	2 (1.8)	7 (6.3)

Events were reported in at least 5% of subjects in either treatment group and are sorted by decreasing frequency in the pregabalin treatment group.
MedDRA (version 13.0) coding used.
MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects.

Treatment-related treatment emergent adverse events (TEAEs) leading to permanent discontinuations are presented in Table 17.

Table 17. Discontinuations Due to Adverse Events

Serial Number	Preferred Term	Severity	Outcome	Causality
1	Dizziness	Severe	Resolved	Study Drug
2	Headache	Moderate	Resolved	Study Drug
3	Euphoric Mood	Mild	Resolved	Study Drug

MedDRA = Medical Dictionary for Regulatory Activities (Version 13.0).

The dose was reduced or temporarily discontinued due to AEs in 28 (25.0%) subjects during pregabalin treatment and in 10 (9.0%) subjects during placebo treatment; all AEs leading to dose reduction or temporary discontinuation were considered treatment-related. The summary of TEAEs resulting in temporary discontinuation or dose reduction is presented in Table 18.

Table 18. Summary of Treatment-Emergent Adverse Events Resulting in Temporary Discontinuation or Dose Reduction Occurring in at Least 2% of Subjects Receiving Either Treatment (All Causalities)

Adverse Event Number (%) of Subjects	Placebo N=111	Pregabalin N=112
Dizziness	2 (1.8)	12 (10.7)
Somnolence	1 (0.9)	7 (6.3)
Headache[a]	5 (4.5)	2 (1.8)
Nausea[a]	2 (1.8)	3 (2.7)

AEs listed in descending order in the pregabalin treatment group.
All AEs listed were considered treatment-related.
MedDRA (version 13.0) coding used.
AEs = adverse events; MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects.
a. One subject reported this AE and had dose reduced or a temporary discontinuation during both crossover periods.

No serious AEs were reported for randomized subjects during the study. There were no deaths reported during the study.

There were no clinically significant physical examination or ECG findings at screening. There were no clinically meaningful vital sign findings for changes from baseline.

Four subjects were randomized twice, and treated simultaneously for at least 2 days at 2 study centers. Two of the subjects were treated concurrently with placebo at 1 study center and pregabalin at a second study center. A third subject received titration doses of pregabalin concurrently at 2 sites for only 2 days; this subject received a total daily dose of 225 mg pregabalin on those 2 days. The fourth subject was treated with pregabalin at 2 study centers concurrently for a total of 21 days. The subject's double randomization was detected only after they had completed the study at both study centers. The total daily dose of pregabalin received by the subject at both study centers during that time ranged from 525 mg to 900 mg, and the subject was exposed to a daily pregabalin dose of 900 mg for a total of 9 consecutive days; however, since no blood samples were taken as part of this study, the total daily dose taken could not be verified. This subject did not report any AEs following either randomization.

A total of 3 unique subjects in placebo treatment and 4 unique subjects in pregabalin treatment reported suicidal ideation (per the C-CASA mapping) during the study. The results of the STS are summarized in Table 19.

Table 19. Columbia Classification Algorithm of Suicide Assessment (C-CASA; Derived From STS; Safety Population)

Timepoint / Category	Placebo n (%)	Pregabalin n (%)
Visit 1 (Screening)		
Number assessed	60	59
Suicide attempt	0	0
Preparatory acts toward imminent suicidal behavior	0	2 (3.4)
Suicidal ideation	5 (8.3)	5 (8.5)
Self-injurious behavior, no suicidal intent	1 (1.7)	0
Visit 4 (start of Period 1)		
Number assessed	60	59
Suicide attempt	0	0
Preparatory acts toward imminent suicidal behavior	0	0
Suicidal ideation	0	1 (1.7)
Self-injurious behavior, no suicidal intent	0	0
Visit 5 (end of Period 1)		
Number assessed	55	53
Suicide attempt	0	0
Preparatory acts toward imminent suicidal behavior	0	0
Suicidal ideation	1 (1.8)	1 (1.9)
Self-injurious behavior, no suicidal intent	0	0
Visit 6 (start of Period 2)		
Number assessed	51	53
Suicide attempt	0	0
Preparatory acts toward imminent suicidal behavior	0	0
Suicidal ideation	2 (3.9)	1 (1.9)
Self-injurious behavior, no suicidal intent	0	0
Visit 7 (end of Period 2)		
Number assessed	49	52
Suicide attempt	0	0
Preparatory acts toward imminent suicidal behavior	0	0
Suicidal ideation	1 (2.0)	1 (1.9)
Self-injurious behavior, no suicidal intent	0	0

Lifetime assessment given at screening; later assessments report results since last visit.
n = number of subjects meeting criterion; STS = suicidality tracking scale.

These findings were not considered AEs by the Investigators and were deemed to not meet the standard necessitating further risk assessment

CONCLUSIONS:

- Pregabalin treatment resulted in significant improvement compared to placebo in sleep maintenance as assessed by the primary efficacy endpoint in the study, WASO derived from polysomnography, following 4 weeks of treatment.

- Pregabalin treatment resulted in significant improvements compared to placebo in sleep maintenance as measured by secondary PSG and subjective endpoints.

- Pregabalin treatment resulted in significant improvements compared to placebo in sleep quality as measured by secondary subjective endpoints.

- Pregabalin was well-tolerated, and adverse event reports were consistent with the known safety profile of pregabalin.