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

PROTOCOL NO.: A0081100

PROTOCOL TITLE: A 14-Week, Randomized, Double-Blind, Placebo-Controlled Trial of Pregabalin Twice Daily in Patients With Fibromyalgia

Study Centers: A total of 72 centers took part in the study and randomized subjects; 4 in Australia, 12 in Canada, 2 in Denmark, 5 in France, 5 in Germany, 4 in India, 5 in Italy, 3 in Republic of Korea, 4 in Mexico, 5 in Netherlands, 4 in Portugal, 4 in Spain, 4 in Sweden, 3 in Switzerland, 3 in Venezuela, and 5 in the United Kingdom.

Study Initiation Date and Final Completion Dates: 31 July 2006 and 20 November 2007

Phase of Development: Phase 3

Study Objectives: The primary objective was to evaluate the efficacy and safety of pregabalin twice daily (BID) compared with placebo for the symptomatic relief of pain in subjects with fibromyalgia.

If the first objective was met, then the second primary objective was to evaluate the efficacy and safety of pregabalin (BID) compared with placebo for the symptomatic relief of pain and improvement of global impressions in subjects with fibromyalgia.

The secondary objective was to evaluate the efficacy of pregabalin (BID) compared with placebo for improvement in sleep, function, fatigue, health-related quality of life, and mood disturbance associated with fibromyalgia.

METHODS

Study Design: This was a 14-week randomized, double-blind, multiple-dose, placebo-controlled, parallel-group, multicenter study. The study comprised a 1-week baseline/placebo run-in phase followed by a 14-week double-blind treatment phase including an initial 2-week titration phase. Subjects with fibromyalgia who demonstrated a high response (≥30% decrease on the pain visual analogue scale [VAS]) to placebo were discontinued from the study at the end of the run-in phase. All qualified subjects were then randomized into 1 of 4 treatment groups: pregabalin 300 mg/day (150 mg BID), 450 mg/day (225 mg BID), 600 mg/day (300 mg BID), or placebo. All pregabalin treatment groups began with a dose of 150 mg/day and titrated to the randomized dose within the first 2 weeks. This was followed by an additional 12 weeks at the fixed, randomized dose (total treatment period duration 14 weeks). During the study, subjects were to return to the clinic for

7 scheduled visits, including screening. At the end of the double-blind phase, all subjects had the option to continue treatment with pregabalin in a 3-month, open-label study. A 1-week follow-up visit (Visit 8) was performed for subjects not entering the open-label study. The schedule of events are summarized in Table 1.

Table 1. Schedule of Events

Study Phase:		**Baseline/Placebo Run-In (1 Week)**	**Double-Blind Treatment (14 Weeks)**						**Follow-Up (1 Week)**
Clinic Visit No.:	**0 [a]**	**1**	**2**	**3**	**4**	**5**	**6**	**7/EOT**	**8/FU[b]**
End of Study Week[c]:	**Washout**	**Screening**	**Randomization**	**Week 2**	**Week 3**	**Week 6**	**Week 10**	**Week 14**	**Week 15**
Day:		**-8**	**-1**	**14**	**21**	**42**	**70**	**98**	**105**
Observation/Procedure									
Informed consent	(X)	X							
Inclusion/exclusion	(X)----------X								
Medical history		X							
Tender point count		X							
Physical examination		X				Vitals only		X	
Abbreviated neurological examination		X						X	
12-Lead ECG		X						X	
Clinical labs: pregnancy test (serum)	(X)	X				X		X	
Clinical labs: hematology, chemistry	(X)	X				X		X	X
Clinical labs: urinalysis	(X)	X						X	X
Clinical labs: ESR at local lab[d]	(X)	X							
Clinical labs: pharmacogenomics						X			
Adverse events			X	X	X	X	X	X	X
Concomitant medications	(X)	X	X	X	X	X	X	X	
Study medication review/dosing/dispensing		X[e]	X[e]	X[e]	X[f]	X	X	X[g]	
Manual tender point survey (MTPS)			X						
Daily diaries (pain and sleep quality)		X----------X							
Patient global impression of change (PGIC)								X	
Short-form 36 (SF-36) health survey			X					X	
Fibromyalgia impact questionnaire (FIQ)			X					X	
Medical outcomes study (MOS) sleep scale			X					X	
Multidimensional assessment of fatigue (MAF)			X					X	
Hospital anxiety and depression scale (HADS)			X					X	
Pain visual analogue scale (VAS)		X	X					X	

ECG = electrocardiogram; EOT = end of treatment; ESR = erythrocyte sedimentation rate; FU = follow-up.

a. Visit 0 was for subjects requiring washout of prohibited medications. Informed consent was obtained prior to washout of any prohibited medication. Laboratory tests could have been performed prior to Visit 1 at Visit 0 for all subjects after the informed consent was signed.
b. The follow-up visit was only for subjects discontinuing study medication and not entering open-label protocol.
c. Telephone contact was made with subjects twice between Visit 2 and Visit 3 and once between subsequent visits to ensure compliance to study procedures.
d. ESR sample was obtained at Visits 0 or 1 if no results were available from the past 6 months.
e. Subjects were instructed to take the study drug from a new dispensed package or bottle on the day following the visit.
f. A new study medication bottle was not dispensed at Visit 4.
g. Open-label medication was dispensed for subjects continuing in the open-label study.

Number of Subjects (Planned and Analyzed): The study was planned to enroll 740 subjects. A total of 986 subjects were screened of which 747 subjects were randomized to treatment (35 in Australia, 165 in Canada, 46 in Denmark, 38 in France, 72 in Germany, 26 in India, 64 in Italy, 44 in Mexico, 42 in Netherlands, 9 in Portugal, 50 in Republic of Korea, 28 in Spain, 48 in Sweden, 18 in Switzerland, 20 in the United Kingdom, and 42 in Venezuela). Of the 747 randomized subjects, 735 subjects received at least one dose of study medication and were analyzed for efficacy and safety.

Diagnosis and Main Criteria for Inclusion: Subjects (males or females at least 18 years old) who met the American College of Rheumatology (ACR) criteria for fibromyalgia with a score of ≥40 mm on the pain visual analog scale (VAS) (at screening and randomization) and had an average pain score of ≥4 on 4 daily pain diaries completed satisfactorily within the previous 7 days at randomization, were eligible for inclusion in the study.

Study Treatment: Study medication was supplied as blinded capsules containing 75, 150, 200, 225 and 300 mg of pregabalin and matching placebo. Eligible subjects were randomized to receive pregabalin or matching placebo capsules orally, 2 capsules daily for 14 weeks (2-week titration phase + 12-week fixed-dose phase) with or without food. Subjects started at 150 mg/day at the beginning of the titration phase. All groups were blinded to the titration. The dosing schedule is provided in Table 2.

Table 2. Dosing Schedule

Placebo Run-In Phase	Treatment Group	Titration Phase				Fixed Dose Phase
Day -7 to Day -1	**Randomization**	**Days 1-3**	**Days 4-8**	**Days 9-11**	**Days 12-14**	**Weeks 3-14**
Placebo BID	Placebo	Placebo BID	Placebo BID	Placebo BID	Placebo BID	Placebo BID
	300 mg/day	75 mg BID	150 mg BID	150 mg BID	150 mg BID	150 mg BID
	450 mg/day	75 mg BID	150 mg BID	200 mg BID	225 mg BID	225 mg BID
	600 mg/day	75 mg BID	150 mg BID	200 mg BID	225 mg BID	300 mg BID

BID = twice daily.

Efficacy Endpoints: Primary Endpoints: The primary endpoint for the first objective was: Endpoint mean pain score, defined as the mean of the last 7 pain diary entries in the study while the subject was on study medication.

If the first objective was positive (efficacy in endpoint mean pain), 1 additional endpoint was assessed for the second objective: Subject global assessment (Patient Global Impression of Change) at termination visit.

Secondary Endpoints: Sleep, fatigue, health-related quality of life, functioning, pain, and mood disturbance were to be assessed using the following instruments:

- Medical Outcomes Study (MOS) Sleep Scale (MOS Sleep Scale);
- Quality of Sleep Score from the Daily Sleep Diary;
- Multidimensional Assessment of Fatigue (MAF);

- Fibromyalgia Impact Questionnaire (FIQ);
- Short-Form 36 Health Survey (SF-36);
- Pain VAS; and
- Hospital Anxiety and Depression Scale (HADS).

Safety Evaluations: All subjects who took at least 1 dose of study medication (Full Analysis Set [FAS] population) were included in the evaluation of safety. Safety was evaluated using frequency and intensity of adverse events (AEs); physical and neurological examinations; 12-lead electrocardiogram (ECG); vital signs and clinical laboratory tests. AEs were monitored throughout the study and examined by nature, intensity, and relationship to treatment.

Statistical Methods: The primary and secondary efficacy analyses were performed on the FAS, defined as all randomized subjects who received at least 1 dose of study medication, regardless of compliance with study medication. All statistical testing was 2-sided and performed at the 0.05 level to determine the efficacy of each treatment arm of pregabalin compared to placebo treatment. The method of last observation carried forward (LOCF) was used for all endpoint analyses.

Endpoint mean pain score, FIQ-total score, MOS Sleep Scale (except Optimal Sleep Score), endpoint mean sleep quality scores, SF-36 Health Survey, FIQ subscales, MAF, VAS and HADS were analyzed using an analysis of covariance (ANCOVA), using treatment, center, and baseline score value as covariates. A Mixed Model Repeated Measures (MMRM) analysis was conducted to examine weekly mean pain and sleep scores and included factors for the fixed, categorical effects of treatment, center, week, treatment-by-week interaction and baseline pain as covariates. PGIC was analyzed using a modified ridit transformation with the Cochran-Mantel-Haenszel (CMH) procedure, adjusting for center. MOS sleep scale optimal sleep domain was analyzed using a logistic regression model, with treatment and study center in the model and optimal sleep at baseline as covariates.

Safety data were summarized descriptively using the FAS. All randomized subjects that took at least 1 dose of study medication were included, regardless of whether there were any post-baseline observations.

RESULTS

Subject Disposition and Demography: A total of 747 subjects were randomized to treatment of which 735 subjects were treated (184 received placebo and 551 received pregabalin). Twelve subjects were randomized but did not take study medication and so were not included in the FAS. Of the 735 subjects who were treated, 518 (70.5%) subjects completed the study and 217 (29.5%) discontinued (Table 3).

Table 3. Summary of Subject Evaluation Groups

Number (%) of Subjects	Placebo	Pregabalin 300 mg/Day	Pregabalin 450 mg/Day	Pregabalin 600 mg/Day	All Pregabalin	All Subjects
Entered screening phase						986
Completed screening phase						746 (75.7)
Withdrawn during screening phase						240 (24.3)
Randomized	189	187	184	187	558	747[a]
Randomized and took study medication	184	183	182	186	551	735
Completed	141 (76.6)	123 (67.2)	133 (73.1)	121 (65.1)	377 (68.4)	518 (70.5)
Discontinued	43 (23.4)	60 (32.8)	49 (26.9)	65 (35.0)	174 (31.6)	217 (29.5)
Adverse event[b]	23 (12.5)	36 (19.7)	38 (20.9)	47 (25.3) [c]	121 (22.0)	144 (19.6)
Lack of efficacy	8 (4.4)	6 (3.3)	3 (1.7)	5 (2.7)	14 (2.5)	22 (3.0)
Lost to follow-up	1 (0.5)	2 (1.1)	2 (1.1)	2 (1.1)	6 (1.1)	7 (1.0)
Withdrawn consent	8 (4.4)	14 (7.7)	4 (2.2)	9 (4.8)	27 (4.9)	35 (4.8)
Other[d]	3 (1.6)	2 (1.1)	2 (1.1)	2 (1.1)	6 (1.1)	9 (1.2)
Analyzed for efficacy:						
FAS	184 (100)	183 (100)	182 (100)	186 (100)	551 (100)	735 (100)
PP	159 (86.4)	140 (76.5)	148 (81.3)	143 (76.9)	431 (78.2)	590 (80.3)
Analyzed for safety:						
Adverse events	184 (100)	183 (100)	182 (100)	186 (100)	551 (100)	735 (100)
Laboratory data[e]	176 (95.7)	169 (92.3)	168 (92.3)	167 (89.8)	504 (91.5)	680 (92.5)

FAS = full analysis set; PP = pre protocol; SAE = serious adverse event.

a. Includes 1 subject who was a screening failure who was randomized in error but who did not receive any treatment.
b. Includes discontinuations due to non-treatment emergent adverse events (3 placebo subjects, 2 pregabalin 300 mg/day subjects, 2 pregabalin 450 mg/day subjects and 1 pregabalin 600 mg/day subject).
c. A SAE of pneumonia for 1 subject resulted in no action taken with respect to study drug (pregabalin 600 mg/day). This was reflected correctly in the SAE tables derived from the clinical safety database. The project safety database incorrectly reported the action taken as discontinued.
d. Other reasons included subjects off medication and missing visits, non-compliance, lack of time for participation, worry about the possibility of adverse events, subject excluded by the Investigator, subject not wanting to participate, and unknown.
e. Fifty five subjects had no baseline or on-treatment laboratory test data.

The demographic characteristics of all subjects are presented in Table 4. No significant differences among treatment groups were observed in any subject demographics or characteristics such as age, gender, height, weight and duration of fibromyalgia.

Table 4. Demographic and Baseline Characteristics – All Subjects

	Placebo	Pregabalin 300 mg/Day	Pregabalin 450 mg/Day	Pregabalin 600 mg/Day	All Pregabalin	All Subjects
	N=184	N=183	N=182	N=186	N=551	N=735
Sex						
Male	16 (8.7%)	17 (9.3%)	13 (7.1%)	17 (9.1%)	47 (8.5%)	63 (8.6%)
Female	168 (91.3%)	166 (90.7%)	169 (92.9%)	169 (90.9%)	504 (91.5%)	672 (91.4%)
Age (years)						
Mean (SD)	48.1 (11.3)	48.4 (10.8)	48.0 (11.3)	49.6 (11.3)	48.7 (11.1)	48.5 (11.2)
Range	20–81	21–71	22–74	25–77	21–77	20–81
Race						
White	141 (76.6%)	142 (77.6%)	136 (74.7%)	139 (74.7%)	417 (75.5%)	558 (75.9%)
Black	0	1 (0.5)	0	0	1 (0.2%)	1 (0.1%)
Hispanic	24 (13.0%)	21 (11.5%)	24 (13.2%)	23 (12.4%)	68 (12.3%)	92 (12.5%)
Other	19 (10.3%)	19 (10.4%)	22 (12.1%)	24 (12.9%)	65 (11.38)	84 (11.4%)
Weight (kg)						
Mean (SD)	72.2 (15)	70.1 (14.6)	74.1 (17.6)	73.5 (16.4)	72.5 (16.3)	72.5 (16)
Range	47.3–129.0	43.0–127.0	40.0–149.7	45.0–140.3	40.0–149.7	40.0–149.7
Duration of fibromyalgia prior to study start (months)						
N	184	183	182	186	551	735
Median	82.5	59.0	61.0	84.5	65.0	71.0
Mean (SD)	107.6 (98.7)	83.5 (80.8)	88.6 (82.5)	115.2 (107.6)	95.9 (92.1)	98.8 (93.9)
Range	3.0–544.0	4.0–471.0	4.0–420.0	3.0–543.0	3.0–543.0	3.0–554.0
Mean, years	9.0	7.0	7.4	9.6	8.0	8.2
Baseline mean pain score[a]						
N	184	183	550	186	550	734
Mean (SD)	6.68 (1.48)	6.76 (1.29)	6.64 (1.33)	6.59 (1.37)	6.64 (1.33)	6.65 (1.36)

N = number of subjects; SD = standard deviation.

a. Baseline = Last 7 available pain scores before taking study medication up to and including Day 1. If less than 7 scores were available then baseline consisted of all scores that were available.

Efficacy Results: Primary Endpoints:

Mean Pain Scores at Endpoint: The single primary endpoint for the first objective was the endpoint mean pain score derived from the subject's daily pain diary. Subjects in all 3 pregabalin groups experienced an improvement (a decrease) in the endpoint mean pain score compared to placebo-treated subjects. Using the ANCOVA model, subjects in the pregabalin 450 mg/day treatment group experienced a statistically significant improvement in the endpoint mean pain score compared to placebo treated subjects, after Hochberg adjustment (mean pain difference of –0.54, adjusted p=0.0164) (Table 5).

Table 5. Endpoint[a] Mean Pain Scores: Results of Analysis of Covariance[b]

Timepoint/ Treatment Group	N	Least Squares			Treatment Comparison (Pregabalin – Placebo)			
		Mean	Mean Change	SE	Difference	95% CI	p-Value	Adjusted p-Value
End of treatment								
Placebo	184	5.93	-0.72	0.14				
PGB 300 mg	183	5.60	-1.05	0.14	-0.34	(-0.72, 0.05)	0.0841	0.1683
PGB 450 mg	181	5.39	-1.26	0.14	-0.54	(-0.92, -0.16)	0.0055*	0.0164**
PGB 600 mg	186	5.70	-0.95	0.14	-0.23	(-0.61, 0.15)	0.2339	0.2339
Interactions treatment by:								
Baseline score p=0.0770								
Cluster/Center (Generalizability) p=0.9575								

* Statistically significant at 5% level.
** Statistically significant at 5% level based on adjusted p-values according to Hochberg's procedure
Scores range from 0-10 with higher scores indicating increased pain.
ANCOVA = analysis of covariance; CI = confidence interval; LS = least squares; N = number of subjects; PGB = pregabalin; SE = standard error.

a. Endpoint mean pain score was the mean of the last 7 daily pain diary ratings while taking the study medication.
b. Based on LS Means using ANCOVA model (including effects for treatment, center and the baseline value as covariate).

A pair-wise comparison, using weekly mean pain scores for each pregabalin treatment group versus the placebo treatment group at each week, was performed to confirm the robustness of the primary endpoint mean pain analysis and evaluate the treatment effect over time. The results of the MMRM analysis of weekly pain scores for Weeks 1 to 14 and also on an overall basis are summarized in Table 6.

Table 6. Weekly[a] Mean Pain Scores: Results of Repeated Measures Analysis of Covariance[b]

Timepoint/ Treatment Group	N	Least Squares			Treatment Comparisons (Pregabalin – Placebo)		
		Mean	Mean Change	SE for Mean Change	Difference	95% CI	p-Value
Week 1							
Placebo	183	6.54	-0.11	0.13			
PGB 300 mg	178	5.85	-0.80	0.14	-0.69	(-1.0, -0.3)	<.0001*
PGB 450 mg	174	5.82	-0.83	0.14	-0.72	(-1.1, -0.4)	<.0001*
PGB 600 mg	178	5.86	-0.79	0.14	-0.68	(-1.0, -0.3)	0.0001*
Week 2							
Placebo	180	6.26	-0.40	0.13			
PGB 300 mg	172	5.65	-1.01	0.14	-0.61	(-1.0, -0.3)	0.0005*
PGB 450 mg	168	5.52	-1.13	0.14	-0.73	(-1.1, -0.4)	<.0001*
PGB 600 mg	174	5.56	-1.09	0.14	-0.68	(-1.0, -0.4)	<.0001*
Week 3							
Placebo	174	6.01	-0.64	0.13			
PGB 300 mg	164	5.47	-1.19	0.14	-0.55	(-0.9, -0.2)	0.0022*
PGB 450 mg	159	5.46	-1.19	0.14	-0.55	(-0.9, -0.2)	0.0022*
PGB 600 mg	163	5.38	-1.27	0.14	-0.63	(-1.0, -0.3)	0.0004*
Week 4							
Placebo	165	6.06	-0.60	0.14			
PGB 300 mg	157	5.40	-1.25	0.14	-0.65	(-1.0, -0.3)	0.0003*
PGB 450 mg	155	5.49	-1.17	0.14	-0.57	(-0.9, -0.2)	0.0017*
PGB 600 mg	156	5.31	-1.34	0.14	-0.75	(-1.1, -0.4)	<.0001*
Week 5							
Placebo	163	6.04	-0.62	0.14			
PGB 300 mg	150	5.40	-1.25	0.14	-0.64	(-1.0, -0.3)	0.0005*
PGB 450 mg	152	5.41	-1.25	0.14	-0.63	(-1.0, -0.3)	0.0006*
PGB 600 mg	148	5.44	-1.22	0.14	-0.60	(-1.0, -0.2)	0.0010*
Week 6							
Placebo	159	5.91	-0.74	0.14			
PGB 300 mg	145	5.38	-1.28	0.14	-0.53	(-0.9, -0.2)	0.0041*
PGB 450 mg	148	5.38	-1.28	0.14	-0.53	(-0.9, -0.2)	0.0042*
PGB 600 mg	144	5.41	-1.24	0.14	-0.50	(-0.9, -0.1)	0.0070*
Week 7							
Placebo	155	5.88	-0.77	0.14			
PGB 300 mg	140	5.53	-1.12	0.14	-0.35	(-0.7, 0.0)	0.0632
PGB 450 mg	144	5.13	-1.53	0.15	-0.75	(-1.1, -0.4)	<.0001*
PGB 600 mg	133	5.36	-1.29	0.15	-0.52	(-0.9, -0.2)	0.0059*
Week 8							
Placebo	149	5.86	-0.80	0.14			
PGB 300 mg	133	5.49	-1.16	0.15	-0.37	(-0.7, 0.0)	0.0561
PGB 450 mg	142	5.13	-1.53	0.15	-0.73	(-1.1, -0.4)	0.0001*
PGB 600 mg	127	5.40	-1.25	0.15	-0.46	(-0.8, -0.1)	0.0173*
Week 9							
Placebo	146	5.77	-0.89	0.14			
PGB 300 mg	128	5.39	-1.27	0.15	-0.38	(-0.8, -0.0)	0.0491*
PGB 450 mg	140	5.21	-1.44	0.15	-0.55	(-0.9, -0.2)	0.0040*
PGB 600 mg	126	5.52	-1.13	0.15	-0.25	(-0.6, 0.1)	0.2022
Week 10							
Placebo	144	5.74	-0.91	0.14			

Table 6. Weekly[a] Mean Pain Scores: Results of Repeated Measures Analysis of Covariance[b]

Timepoint/ Treatment Group	N	Least Squares			Treatment Comparisons (Pregabalin – Placebo)		
		Mean	Mean Change	SE for Mean Change	Difference	95% CI	p-Value
PGB 300 mg	125	5.37	-1.29	0.15	-0.38	(-0.8, 0.0)	0.0570
PGB 450 mg	139	5.17	-1.48	0.15	-0.57	(-1.0, -0.2)	0.0034*
PGB 600 mg	126	5.37	-1.28	0.15	-0.37	(-0.8, 0.0)	0.0602
Week 11							
Placebo	143	5.74	-0.92	0.15			
PGB 300 mg	123	5.37	-1.29	0.15	-0.37	(-0.8, 0.0)	0.0634
PGB 450 mg	137	5.09	-1.56	0.15	-0.64	(-1.0, -0.3)	0.0010*
PGB 600 mg	121	5.46	-1.20	0.16	-0.28	(-0.7, 0.1)	0.1608
Week 12							
Placebo	141	5.77	-0.88	0.15			
PGB 300 mg	121	5.51	-1.15	0.16	-0.26	(-0.7, 0.1)	0.1912
PGB 450 mg	135	5.15	-1.50	0.15	-0.62	(-1.0, -0.2)	0.0019*
PGB 600 mg	119	5.38	-1.27	0.16	-0.39	(-0.8, 0.0)	0.0563
Week 13							
Placebo	140	5.88	-0.78	0.15			
PGB 300 mg	120	5.41	-1.24	0.16	-0.46	(-0.9, -0.1)	0.0228*
PGB 450 mg	133	5.23	-1.43	0.15	-0.65	(-1.0, -0.3)	0.0011*
PGB 600 mg	118	5.47	-1.18	0.16	-0.40	(-0.8, -0.0)	0.0496*
Week 14							
Placebo	134	5.87	-0.79	0.15			
PGB 300 mg	115	5.32	-1.33	0.16	-0.54	(-0.9, -0.1)	0.0087*
PGB 450 mg	128	5.16	-1.49	0.15	-0.71	(-1.1, -0.3)	0.0005*
PGB 600 mg	111	5.49	-1.16	0.16	-0.37	(-0.8, 0.0)	0.0735
Overall							
Placebo	183	5.95	-0.70	0.11			
PGB 300 mg	178	5.47	-1.19	0.11	-0.48	(-0.8, -0.2)	0.0004*
PGB 450 mg	174	5.31	-1.34	0.11	-0.64	(-0.9, -0.4)	<.0001*
PGB 600 mg	178	5.46	-1.20	0.11	-0.49	(-0.8, -0.2)	0.0003*

* Statistically significant at 5% level.
Scores range from 0-10 with higher scores indicating increased pain.
Overall = analysis of the entire time course of study.
ANCOVA = analysis of covariance; CI = confidence interval; N = number of subjects; PGB = pregabalin; SE = standard error.
a. Week 1, 2, etc. All data for all subjects who entered the week of interest were used in the analysis.
b. Based on least square means using Mixed Model Repeated Measures ANCOVA with effects for treatment, center, week, treatment by week and the baseline value as covariate.

As the first primary objective (pain associated with fibromyalgia) was positive, an additional endpoint was assessed to meet the second primary objective ("management of fibromyalgia"): the PGIC.

Patient Global Impression of Change (PGIC): Statistically significant differences in the PGIC response, favoring pregabalin, were observed for the 450 mg/day and 600 mg/day treatment groups when compared to placebo. The summary of PGIC results at endpoint are presented in Table 7.

Table 7. Summary of Patient Global Impression of Change at Endpoint

Subject Status, n (%)	Placebo	Pregabalin 300 mg/day	Pregabalin 450 mg/day	Pregabalin 600 mg/day
	N=184	N=183	N=182	N=186
Number assessed[a]	169	162	165	155
Any improvement				
Very much improved	7 (4.1)	13 (8.0)	16 (9.7)	20 (12.9)
Much improved	43 (25.4)	45 (27.8)	50 (30.3)	46 (29.7)
Minimally improved	45 (26.6)	50 (30.9)	55 (33.3)	41 (26.5)
No change	43 (25.4)	27 (16.7)	27 (16.4)	25 (16.1)
Any worsening				
Minimally worse	11 (6.5)	9 (5.6)	7 (4.2)	10 (6.5)
Much worse	17 (10.1)	13 (8.0)	8 (4.8)	10 (6.5)
Very much worse	3 (1.8)	5 (3.1)	2 (1.2)	3 (1.9)
Comparison of pregabalin treatment groups to placebo				
p-values[b]	N/A	0.0539	0.0017*	0.0227*

* Statistically significant at the 5% level.
CMH = cochran-mantel-haenszel; N = number of subjects; n = number of subjects in each category; N/A = not applicable.
a. Numbers of subjects with available data for this analysis.
b. Based on CMH test.

Secondary Endpoints: MOS Sleep Scale – Sleep Disturbance: All 3 pregabalin treatment groups showed a statistically significant improvement in MOS Sleep Scale Sleep Disturbance subscale, MOS Overall Sleep Problem Index and Awaken Short of Breath or with Headache subscale when compared to placebo. The results of MOS sleep scale scores are presented in Table 8.

Table 8. Endpoint Results of Analysis of MOS Sleep Scale Scores: Results of Analysis of Covariance [a]

Efficacy Measure/ Treatment Group	N	Least Squares			Treatment Comparison (Pregabalin – Placebo)		
		Mean	Mean Change	SE	Difference	95% CI	p-Value[a]
Sleep disturbance							
Placebo	183	54.47	-5.98	1.79			
PGB 300 mg	182	47.14	-13.31	1.79	-7.32	(-12.20, -2.45)	0.0033*
PGB 450 mg	177	41.18	-19.27	1.84	-13.29	(-18.19, -8.39)	<.0001*
PGB 600 mg	185	41.74	-18.71	1.78	-12.73	(-17.58, -7.87)	<.0001*
Snoring							
Placebo	172	31.33	-0.03	1.75			
PGB 300 mg	174	32.54	1.17	1.73	1.21	(-3.53, 5.95)	0.6165
PGB 450 mg	174	36.25	4.89	1.75	4.92	(0.19, 9.66)	0.0414*
PGB 600 mg	177	37.23	5.87	1.73	5.90	(1.19, 10.61)	0.0142*
Awaken short of breath or with headache							
Placebo	182	35.85	-0.64	1.92			
PGB 300 mg	181	26.69	-9.80	1.91	-9.16	(-14.38, -3.95)	0.0006*
PGB 450 mg	177	23.91	-12.58	1.96	-11.94	(-17.18, -6.70)	<.0001*
PGB 600 mg	184	26.61	-9.88	1.91	-9.24	(-14.43, -4.05)	0.0005*
Quantity of sleep							
Placebo	182	5.93	0.40	0.10			
PGB 300 mg	181	6.14	0.62	0.10	0.21	(-0.07, 0.49)	0.1385
PGB 450 mg	175	6.43	0.91	0.11	0.50	(0.22, 0.79)	0.0005*
PGB 600 mg	182	6.29	0.76	0.10	0.36	(0.08, 0.64)	0.0124*
Sleep adequacy							
Placebo	183	32.25	7.61	1.93			
PGB 300 mg	182	34.69	10.06	1.93	2.45	(-2.81, 7.70)	0.3607
PGB 450 mg	179	41.38	16.75	1.96	9.13	(3.87, 14.40)	0.0007*
PGB 600 mg	185	36.63	12.00	1.92	4.39	(-0.84, 9.61)	0.0999
Somnolence							
Placebo	182	42.65	-0.09	1.50			
PGB 300 mg	181	43.33	0.58	1.50	0.67	(-3.41, 4.76)	0.7456
PGB 450 mg	177	43.35	0.60	1.53	0.70	(-3.40, 4.79)	0.7392
PGB 600 mg	184	44.66	1.91	1.49	2.00	(-2.06, 6.07)	0.3329
Overall sleep problem index							
Placebo	181	53.38	-4.82	1.35			
PGB 300 mg	180	48.95	-9.24	1.35	-4.42	(-8.09, -0.75)	0.0182*
PGB 450 mg	174	45.13	-13.07	1.39	-8.25	(-11.95, -4.56)	<.0001*
PGB 600 mg	184	46.47	-11.73	1.34	-6.91	(-10.56, -3.27)	0.0002*

* Statistically significant at the 5% level.
MOS-Sleep Scale is scored from 0-100 except for the sleep quantity subscale which is scored from 0-24 indicating the number of hours of sleep. Higher scores indicate more of the attribute named in the subscale.
ANCOVA = analysis of covariance; CI = confidence interval; MOS = medical outcomes study; N = number of subjects; PGB = pregabalin; SE = standard error.
a. Based on least square means using ANCOVA model (including effects for treatment, center and the baseline value as covariate).

FIQ Total Score: Using the ANCOVA model, subjects in the pregabalin 450 mg/day treatment group showed a statistically significant improvement in the FIQ total score at

endpoint compared to placebo-treated subjects. The results of FIQ total scores at endpoint are presented in Table 9.

Table 9. Fibromyalgia Impact Questionnaire Total Scores at Endpoint: Results of Analysis of Covariance

Time Point/ Treatment Group	N	Least Squares			Treatment Comparison (Pregabalin – Placebo)		
		Mean	Mean Change	SE	Difference	95% CI	p-Value[a]
End of treatment							
Placebo	184	54.13	-6.94	1.30			
PGB 300 mg	183	52.79	-8.28	1.29	-1.34	(-4.86, 2.17)	0.4540
PGB 450 mg	179	48.26	-12.80	1.32	-5.87	(-9.40, -2.34)	0.0012*
PGB 600 mg	186	52.67	-8.40	1.28	-1.46	(-4.96, 2.04)	0.4120

* Statistically significant at the 5% level.
Scores range from 0 to 100 with higher scores indicating more impairment.
ANCOVA = analysis of covariance; CI = confidence interval; N = number of subjects; PGB = pregabalin; SE = standard error.
a. Based on least square means using ANCOVA model (including effects for treatment, center and the baseline value as covariate).

The following FIQ subscales showed statistically significant differences (decreases) from placebo at endpoint: for pregabalin 450 mg/day: Feel Good, Work Missed, Do Work, Pain, Fatigue, Rested, Depression and Anxiety (Table 10).

Table 10. FIQ Scores at Endpoint: Results of Analysis of Covariance[a]

Efficacy Measure/ Treatment Group	N	Least Squares			Treatment Comparison (Pregabalin – Placebo)		
		Mean	Mean Change	SE	Difference	95% CI	p-Value
FIQ physical impairment							
Placebo	183	3.80	-0.08	0.14			
PGB 300 mg	183	3.60	-0.28	0.14	-0.19	(-0.56, 0.18)	0.3049
PGB 450 mg	179	3.53	-0.35	0.14	-0.26	(-0.63, 0.11)	0.1658
PGB 600 mg	186	3.62	-0.26	0.14	-0.17	(-0.54, 0.20)	0.3579
FIQ feel good							
Placebo	182	6.45	-1.15	0.22			
PGB 300 mg	183	6.50	-1.09	0.22	0.05	(-0.54, 0.65)	0.8599
PGB 450 mg	178	5.82	-1.77	0.22	-0.63	(-1.23, -0.02)	0.0414*
PGB 600 mg	183	6.33	-1.26	0.22	-0.11	(-0.71, 0.49)	0.7107
FIQ work missed							
Placebo	182	3.07	-0.13	0.19			
PGB 300 mg	180	2.88	-0.32	0.19	-0.18	(-0.69, 0.32)	0.4752
PGB 450 mg	178	2.45	-0.75	0.19	-0.62	(-1.12, -0.11)	0.0168*
PGB 600 mg	184	2.93	-0.27	0.18	-0.14	(-0.64, 0.36)	0.5854
FIQ do work							
Placebo	182	5.80	-0.90	0.18			
PGB 300 mg	182	5.64	-1.05	0.18	-0.16	(-0.64, 0.33)	0.5205
PGB 450 mg	179	5.09	-1.60	0.18	-0.71	(-1.19, -0.22)	0.0043*
PGB 600 mg	185	5.71	-0.99	0.18	-0.09	(-0.57, 0.39)	0.7121
FIQ pain							
Placebo	183	6.24	-0.97	0.17			
PGB 300 mg	183	6.00	-1.21	0.17	-0.24	(-0.70, 0.23)	0.3146
PGB 450 mg	179	5.49	-1.72	0.17	-0.75	(-1.22, -0.29)	0.0016*
PGB 600 mg	185	6.10	-1.11	0.17	-0.14	(-0.60, 0.32)	0.5559
FIQ fatigue							
Placebo	183	6.74	-0.81	0.18			
PGB 300 mg	183	6.69	-0.86	0.18	-0.06	(-0.55, 0.43)	0.8191
PGB 450 mg	179	6.19	-1.36	0.18	-0.56	(-1.05, -0.06)	0.0286*
PGB 600 mg	184	6.50	-1.05	0.18	-0.24	(-0.73, 0.25)	0.3281
FIQ rested							
Placebo	183	6.64	-0.94	0.19			
PGB 300 mg	183	6.39	-1.19	0.19	-0.24	(-0.77, 0.27)	0.3467
PGB 450 mg	179	6.10	-1.47	0.20	-0.75	(-1.06, -0.01)	0.0461*
PGB 600 mg	185	6.17	-1.41	0.19	-0.14	(-0.99, 0.05)	0.0790
FIQ stiffness							
Placebo	183	6.20	-1.06	0.18			
PGB 300 mg	183	6.19	-1.06	0.18	-0.00	(-0.49, 0.48)	0.9849
PGB 450 mg	179	5.97	-1.28	0.18	-0.22	(-0.71, 0.26)	0.3666
PGB 600 mg	185	6.32	-0.94	0.18	0.12	(-0.37, 0.60)	0.6328
FIQ anxiety							
Placebo	183	4.86	-0.48	0.20			
PGB 300 mg	183	4.66	-0.68	0.20	-0.19	(-0.73, 0.34)	0.4740
PGB 450 mg	179	4.21	-1.13	0.20	-0.64	(-1.18, -0.11)	0.0186*
PGB 600 mg	185	4.66	-0.68	0.20	-0.20	(-0.73, 0.33)	0.4633
FIQ depression							
Placebo	181	4.53	-0.22	0.20			
PGB 300 mg	183	4.17	-0.58	0.20	-0.36	(-0.91, 0.18)	0.1918
PGB 450 mg	179	3.56	-1.19	0.20	-0.97	(-1.52, -0.42)	0.0006*
PGB 600 mg	184	4.32	-0.43	0.20	-0.21	(-0.75, 0.34)	0.4554

Table 10. FIQ Scores at Endpoint: Results of Analysis of Covariance[a]

Efficacy Measure/ Treatment Group	N	Least Squares			Treatment Comparison (Pregabalin – Placebo)		
		Mean	Mean Change	SE	Difference	95% CI	p-Value

[*] Statistically significant at the 5% level.
All FIQ subscales are scored from 0-10 with higher scores indicating more impairment in the subscale attribute.
ANCOVA = analysis of covariance; CI = confidence interval; FIQ = fibromyalgia impact questionnaire; N = number of subjects; PGB = pregabalin; SE = standard error.
a. Based on least square means using ANCOVA model (including effects for treatment, center and the baseline value as covariate).

Daily Sleep Diary: Sleep Quality Scores: At endpoint, statistically significant improvements were seen for mean sleep quality score for subjects in all 3 pregabalin treatment groups compared with subjects who received placebo treatment (Table 11).

Table 11. Endpoint[a] Mean Sleep Quality: Results of Analysis of Covariance

Time Point/ Treatment Group	N	Least Squares			Treatment Comparison (Pregabalin – Placebo)		
		Mean	Mean Change	SE	Difference	95% CI	p-Value[b]
End of treatment							
Placebo	184	5.01	-0.94	0.15			
PGB 300 mg	183	4.50	-1.45	0.15	-0.51	(-0.92, -0.10)	0.0151[*]
PGB 450 mg	181	4.23	-1.72	0.15	-0.78	(-1.19, -0.37)	0.0002[*]
PGB 600 mg	186	4.00	-1.95	0.15	-1.01	(-1.42, -0.60)	<.0001[*]

[*] Statistically significant at the 5% level.
Scores range from 0-10 with higher scores indicating decreased sleep quality.
ANCOVA = analysis of covariance; CI = confidence interval; N = number of subjects; PGB = pregabalin; SE = standard error.
a. Endpoint = Last 7 available scores while on study medication.
b. Based on least square means using ANCOVA model (including effects for treatment, center and the baseline value as covariate).

All 3 pregabalin treatment groups showed a statistically significant improvement in sleep quality (a decrease) at endpoint and at each week from Weeks 1 to 14 inclusive, with the exception of the 300 mg/day pregabalin group at Week 12 when statistical significance was not reached (Table 12).

Table 12. Weekly[a] Mean Sleep Quality Scores: Results of Repeated Measures Analysis of Covariance[b]

Period/ Treatment Group (mg/day)	N	Least Squares			Treatment Comparison (Pregabalin – Placebo)		
		Mean	Mean Change	SE	Difference	95% CI	p-Value
Week 1							
Placebo	183	5.58	-0.38	0.14			
PGB 300 mg	178	4.74	-1.22	0.15	-0.84	(-1.2, -0.5)	<.0001*
PGB 450 mg	174	4.88	-1.08	0.15	-0.70	(-1.1, -0.3)	0.0003*
PGB 600 mg	178	4.73	-1.23	0.15	-0.85	(-1.2, -0.5)	<.0001*
Week 2							
Placebo	180	5.34	-0.62	0.14			
PGB 300 mg	172	4.46	-1.50	0.15	-0.88	(-1.3, -0.5)	<.0001*
PGB 450 mg	168	4.53	-1.43	0.15	-0.81	(-1.2, -0.4)	<.0001*
PGB 600 mg	174	4.37	-1.59	0.15	-0.97	(-1.3, -0.6)	<.0001*
Week 3							
Placebo	174	5.21	-0.75	0.14			
PGB 300 mg	164	4.52	-1.44	0.15	-0.69	(-1.1, -0.3)	0.0004*
PGB 450 mg	159	4.40	-1.56	0.15	-0.81	(-1.2, -0.4)	<.0001*
PGB 600 mg	163	4.06	-1.90	0.15	-1.15	(-1.5, -0.8)	<.0001*
Week 4							
Placebo	165	5.23	-0.73	0.15			
PGB 300 mg	157	4.42	-1.54	0.15	-0.81	(-1.2, -0.4)	<.0001*
PGB 450 mg	155	4.29	-1.67	0.15	-0.95	(-1.3, -0.6)	<.0001*
PGB 600 mg	156	3.95	-2.01	0.15	-1.29	(-1.7, -0.9)	<.0001*
Week 5							
Placebo	163	5.14	-0.82	0.15			
PGB 300 mg	150	4.28	-1.68	0.15	-0.87	(-1.3, -0.5)	<.0001*
PGB 450 mg	152	4.27	-1.69	0.15	-0.87	(-1.3, -0.5)	<.0001*
PGB 600 mg	148	3.97	-1.99	0.15	-1.17	(-1.6, -0.8)	<.0001*
Week 6							
Placebo	159	5.12	-0.84	0.15			
PGB 300 mg	145	4.38	-1.58	0.15	-0.73	(-1.1, -0.3)	0.0002*
PGB 450 mg	148	4.20	-1.76	0.16	-0.92	(-1.3, -0.5)	<.0001*
PGB 600 mg	144	3.81	-2.15	0.16	-1.31	(-1.7, -0.9)	<.0001*
Week 7							
Placebo	155	5.05	-0.91	0.15			
PGB 300 mg	140	4.45	-1.51	0.16	-0.60	(-1.0, -0.2)	0.0031*
PGB 450 mg	144	4.12	-1.84	0.16	-0.93	(-1.3, -0.5)	<.0001*
PGB 600 mg	133	3.76	-2.20	0.16	-1.29	(-1.7, -0.9)	<.0001*
Week 8							
Placebo	149	4.97	-0.99	0.15			
PGB 300 mg	133	4.35	-1.61	0.16	-0.62	(-1.0, -0.2)	0.0026*
PGB 450 mg	142	4.01	-1.95	0.16	-0.97	(-1.4, -0.6)	<.0001*
PGB 600 mg	127	3.71	-2.25	0.16	-1.27	(-1.7, -0.9)	<.0001*
Week 9							
Placebo	146	4.85	-1.11	0.15			
PGB 300 mg	128	4.31	-1.65	0.16	-0.54	(-1.0, -0.1)	0.0101*
PGB 450 mg	140	4.02	-1.94	0.16	-0.83	(-1.2, -0.4)	<.0001*
PGB 600 mg	126	3.72	-2.24	0.16	-1.13	(-1.5, -0.7)	<.0001*
Week 10							
Placebo	144	4.82	-1.14	0.16			

Table 12. Weekly[a] Mean Sleep Quality Scores: Results of Repeated Measures Analysis of Covariance[b]

Period/ Treatment Group (mg/day)	N	Least Squares			Treatment Comparison (Pregabalin – Placebo)		
		Mean	Mean Change	SE	Difference	95% CI	p-Value
PGB 300 mg	125	4.20	-1.76	0.16	-0.62	(-1.0, -0.2)	0.0035*
PGB 450 mg	139	3.93	-2.04	0.16	-0.90	(-1.3, -0.5)	<.0001*
PGB 600 mg	126	3.62	-2.34	0.17	-1.20	(-1.6, -0.8)	<.0001*
Week 11							
Placebo	143	4.87	-1.09	0.16			
PGB 300 mg	123	4.31	-1.65	0.17	-0.56	(-1.0, -0.1)	0.0093*
PGB 450 mg	137	4.04	-1.92	0.16	-0.83	(-1.2, -0.4)	<.0001*
PGB 600 mg	121	3.72	-2.24	0.17	-1.15	(-1.6, -0.7)	<.0001*
Week 12							
Placebo	141	4.74	-1.22	0.16			
PGB 300 mg	121	4.34	-1.62	0.17	-0.40	(-0.8, 0.0)	0.0631
PGB 450 mg	135	4.01	-1.95	0.16	-0.73	(-1.2, -0.3)	0.0006*
PGB 600 mg	119	3.67	-2.29	0.17	-1.07	(-1.5, -0.6)	<.0001*
Week 13							
Placebo	140	4.91	-1.05	0.16			
PGB 300 mg	120	4.29	-1.67	0.17	-0.62	(-1.1, -0.2)	0.0048*
PGB 450 mg	133	4.03	-1.93	0.17	-0.88	(-1.3, -0.5)	<.0001*
PGB 600 mg	118	3.70	-2.26	0.17	-1.22	(-1.6, -0.8)	<.0001*
Week 14							
Placebo	134	4.88	-1.08	0.16			
PGB 300 mg	115	4.22	-1.74	0.17	-0.66	(-1.1, -0.2)	0.0031*
PGB 450 mg	128	4.01	-1.95	0.17	-0.87	(-1.3, -0.4)	<.0001*
PGB 600 mg	111	3.67	-2.29	0.18	-1.21	(-1.7, -0.8)	<.0001*
Overall							
Placebo	183	5.05	-0.91	0.12			
PGB 300 mg	178	4.38	-1.58	0.12	-0.67	(-1.0, -0.4)	<.0001*
PGB 450 mg	174	4.19	-1.77	0.12	-0.86	(-1.1, -0.6)	<.0001*
PGB 600 mg	178	3.89	-2.07	0.12	-1.16	(-1.5, -0.9)	<.0001*

* Statistically significant at the 5% level.
Scores range from 0-10 with higher scores indicating decreased sleep quality.
ANCOVA = analysis of covariance; CI = confidence interval; N = number of subjects; PGB = pregabalin; SE = standard error.
a. Weeks 1, 2, etc. All data for all subjects who entered the week of interest were used in the analysis.
b. Based on least square means using mixed model repeated measures ANCOVA model (including effects for treatment, center, treatment by week and the baseline value as covariate).

Multidimensional Assessment of Fatigue: There were no statistically significant differences among any of the 3 pregabalin treatment groups and the placebo treatment group for this efficacy measure at endpoint (Table 13).

Table 13. MAF Global Index: Results of Analysis of Covariance[a]

Efficacy Measure/ Treatment Group	N	Least Squares			Treatment Comparison (Pregabalin – Placebo)		
		Mean	Mean Change	SE	Difference	95% CI	p-Value
Global fatigue index							
Placebo	183	32.77	-1.90	0.62			
PGB 300 mg	175	31.85	-2.83	0.63	-0.92	(-2.63, 0.78)	0.2885
PGB 450 mg	175	31.36	-3.32	0.64	-1.42	(-3.12, 0.29)	0.1028
PGB 600 mg	181	32.48	-2.20	0.62	-0.30	(-1.99, 1.39)	0.7299

MAF Fatigue Global Fatigue Index scores range from 1-50 with higher scores indicating increased fatigue.
ANCOVA = analysis of covariance; CI = confidence interval; MAF = multidimensional assessment of fatigue; N = number of subjects; PGB = pregabalin; SE = standard error.

a. Based on least square means using ANCOVA model (including effects for treatment, center and the baseline value as covariate).

SF-36 Health Survey: The following SF-36 Health Survey domain scores showed statistically significant differences (increases) from placebo at endpoint (Table 14): Pregabalin 300 mg/day - Mental Component Score; pregabalin 450 mg/day – Emotional Role Limitations, Social Functioning, Mental Health, Bodily Pain, Vitality and Mental Component Score; and pregabalin 600 mg/day - Mental Health and Mental Component Score.

Table 14. SF-36 Health Survey at Endpoint: Results of Analysis of Covariance[a]

Efficacy Measure / Treatment Group	N	Least Squares			Treatment Comparison (Pregabalin – Placebo)		
		Mean	Mean Change	SE	Difference	95% CI	p-Value
Physical functioning							
Placebo	184	48.10	4.64	1.32			
PGB 300 mg	183	48.77	5.30	1.31	0.66	(-2.91, 4.24)	0.7154
PGB 450 mg	177	50.10	6.63	1.35	1.99	(-1.61, 5.60)	0.2775
PGB 600 mg	186	47.60	4.14	1.31	-0.50	(-4.06, 3.07)	0.7844
Physical role limitations							
Placebo	183	43.72	4.01	1.64			
PGB 300 mg	182	44.24	4.54	1.63	0.53	(-3.91, 4.97)	0.8157
PGB 450 mg	177	45.22	5.51	1.67	1.50	(-2.96, 5.97)	0.5089
PGB 600 mg	185	44.74	5.03	1.62	1.02	(-3.39, 5.44)	0.6500
Emotional role limitations							
Placebo	183	58.46	-2.31	1.94			
PGB 300 mg	182	62.53	1.77	1.94	4.07	(-1.19, 9.34)	0.1292
PGB 450 mg	177	64.73	3.96	1.98	6.27	(0.97, 11.56)	0.0204*
PGB 600 mg	185	62.36	1.59	1.92	3.90	(-1.34, 9.14)	0.1444
Social functioning							
Placebo	183	55.50	0.72	1.77			
PGB 300 mg	183	59.10	4.32	1.77	3.60	(-1.22, 8.42)	0.1429
PGB 450 mg	178	60.53	5.75	1.81	5.03	(0.19, 9.87)	0.0418*
PGB 600 mg	186	58.37	3.59	1.76	2.87	(-1.92, 7.66)	0.2403
Mental health							
Placebo	183	55.13	-1.68	1.35			
PGB 300 mg	183	58.68	1.87	1.34	3.55	(-0.12, 7.21)	0.0580
PGB 450 mg	178	61.08	4.27	1.38	5.95	(2.27, 9.64)	0.0016*
PGB 600 mg	186	59.24	2.43	1.34	4.11	(0.46, 7.76)	0.0274*
Bodily pain							
Placebo	183	33.70	4.95	1.31			
PGB 300 mg	183	36.55	7.79	1.30	2.85	(-0.70, 6.40)	0.1155
PGB 450 mg	178	39.07	10.31	1.33	5.37	(1.80, 8.94)	0.0032*
PGB 600 mg	186	36.29	7.54	1.30	2.59	(-0.94, 6.12)	0.1505
Vitality							
Placebo	183	31.79	4.15	1.42			
PGB 300 mg	183	32.89	5.25	1.41	1.10	(-2.75, 4.95)	0.5742
PGB 450 mg	178	36.92	9.28	1.44	5.13	(1.26, 9.00)	0.0095*
PGB 600 mg	186	34.93	7.29	1.41	3.14	(-0.69, 6.97)	0.1076
General health perception							
Placebo	183	44.43	0.92	1.16			
PGB 300 mg	183	46.29	2.79	1.15	1.86	(-1.27, 5.00)	0.2431
PGB 450 mg	177	47.17	3.66	1.18	2.74	(-0.43, 5.90)	0.0898
PGB 600 mg	186	45.71	2.21	1.14	1.28	(-1.84, 4.41)	0.4200
Mental component score							
Placebo	182	39.17	-1.27	0.81			
PGB 300 mg	182	41.49	1.05	0.81	2.32	(0.12, 4.52)	0.0388*
PGB 450 mg	176	42.85	2.41	0.83	3.68	(1.46, 5.89)	0.0012*
PGB 600 mg	184	41.81	1.37	0.80	2.64	(0.45, 4.83)	0.0184*
Physical component score							
Placebo	182	34.83	2.47	0.52			
PGB 300 mg	182	34.95	2.59	0.52	0.12	(-1.29, 1.53)	0.8653
PGB 450 mg	176	35.37	3.00	0.53	0.54	(-0.88, 1.96)	0.4573
PGB 600 mg	184	34.69	2.33	0.52	-0.13	(-1.54, 1.27)	0.8521

Table 14. SF-36 Health Survey at Endpoint: Results of Analysis of Covariance[a]

* Statistically significant at the 5% level.
SF-36 scored from 0-100 with higher scores reflecting better subject status.
ANCOVA = analysis of covariance; CI = confidence interval; N = number of subjects; PGB = pregabalin; SE = standard error; SF = short form.
a. Based on least square means using ANCOVA model (including effects for treatment, center and the baseline value as covariate).

Hospital Anxiety and Depression Scale: In the analysis of the HADS data, none of the treatment comparisons of pregabalin with placebo for either the anxiety or the depression subscale reached statistical significance (Table 15).

Table 15. Endpoint Analysis of HADS Scores[a]

Efficacy Measure/ Treatment Group	N	Least Squares			Treatment Comparison (Pregabalin – Placebo)		
		Mean	Mean Change	SE	Difference	95% CI	p-Value
HADS anxiety total							
Placebo	182	8.56	-0.30	0.25			
PGB 300 mg	180	8.42	-0.44	0.25	-0.14	(-0.83, 0.55)	0.6907
PGB 450 mg	176	8.05	-0.81	0.26	-0.51	(-1.20, 0.19)	0.1536
PGB 600 mg	185	7.96	-0.90	0.25	-0.60	(-1.28, 0.09)	0.0879
HADS depression total							
Placebo	182	7.40	-0.11	0.24			
PGB 300 mg	180	7.17	-0.34	0.24	-0.23	(-0.88, 0.42)	0.4917
PGB 450 mg	176	6.81	-0.70	0.25	-0.59	(-1.25, 0.06)	0.0763
PGB 600 mg	185	7.55	0.04	0.24	0.15	(-0.50, 0.80)	0.6538

HADS anxiety and depression subscale scores range from 0-21 with higher scores indicating greater severity of the subscale condition.
ANCOVA = analysis of covariance; CI = confidence interval; HADS = hospital anxiety and depression scale; N = number of subjects; PGB = pregabalin; SE = standard error.
a. Based on least square means using ANCOVA model (including effects for treatment, center and the baseline value as covariate).

Pain Visual Analogue Scale Scores: Although the pregabalin treated groups improved more than the placebo treated group, in the analysis of the VAS data, only pregabalin 450 mg/day showed a statistically significant reduction in the mean pain VAS score compared with placebo (Table 16).

Table 16. Endpoint Analysis Pain VAS Scores: Results of Analysis of Covariance[a]

Treatment Group	N	Least Squares			Treatment Comparison (Pregabalin – Placebo)		
		Mean	Mean Change	SE	Difference	95% CI	p-Value
Placebo	184	61.56	-10.31	1.67			
PGB 300 mg	183	58.72	-13.15	1.67	-2.84	(-7.38, 1.70)	0.2195
PGB 450 mg	181	54.10	-17.77	1.69	-7.47	(-12.02, -2.91)	0.0013*
PGB 600 mg	186	60.12	-11.75	1.66	-1.44	(-5.97, 3.08)	0.5312

* Statistically significant at the 5% level.
Pain VAS scores ranged from 0 "no pain" to 100 "worst possible pain".
ANCOVA = analysis of covariance; CI = confidence interval; N = number of subjects; PGB = pregabalin; SE = standard error; VAS = visual analogue scale.
a. Based on least square means using ANCOVA model (including effects for treatment, center, and the baseline value as covariate).

Safety Results: An overview of all causality and treatment related AEs is presented in Table 17.

Table 17. Overview of Treatment-Emergent Adverse Events

Number (%) of Subjects	Placebo N=184	Pregabalin 300 mg/Day N=183	Pregabalin 450 mg/Day N=182	Pregabalin 600 mg/Day N=186	All Pregabalin N=551
All causality					
Number of adverse events	433	645	630	710	1985
Subjects with:					
Adverse events	135 (73.4)	155 (84.7)	164 (90.1)	171 (91.9)	490 (88.9)
SAEs	4 (2.2)	2 (1.1)	8 (4.4)	4 (2.2)	14 (2.5)
Severe adverse events	12 (6.5)	32 (17.5)	26 (14.3)	30 (16.1)	88 (16.0)
Discontinuations due to adverse events	20 (10.9)	34 (18.6)	36 (19.8)	48 (25.8)	118 (21.4)
Dose reductions/ temporary discontinuations due to adverse events	3 (1.6)	6 (3.3)	10 (5.5)	13 (7.0)	29 (5.3)
Treatment related adverse events					
Number of adverse events	221	417	397	470	1284
Subjects with:					
Adverse events	89 (48.4)	132 (72.1)	139 (76.4)	157 (84.4)	428 (77.7)
SAEs	0	0	1 (0.5)	0	1 (0.2)
Severe adverse events	6 (3.3)	19 (10.4)	17 (9.3)	19 (10.2)	55 (10.0)
Discontinuations due to adverse events	12 (6.5)	30 (16.4)	30 (16.5)	43 (23.1)	103 (18.7)
Dose reductions/ temporary discontinuations due to adverse events	2 (1.1)	5 (2.7)	7 (3.8)	11 (5.9)	23 (4.2)

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

The treatment-emergent non serious AEs in ≥5% of subjects are summarized in Table 18.

Table 18. Treatment-Emergent Non Serious Adverse Events in ≥5% of Subjects by System Organ Class and Preferred Term (All Causalities)

	Placebo n (%)	Pregabalin 300 mg/Day n (%)	Pregabalin 450 mg/Day n (%)	Pregabalin 600 mg/Day n (%)
Number (%) of subjects:				
Evaluable for adverse events	184	184	182	186
With adverse events	97 (52.7)	137 (74.5)	141 (77.5)	154 (82.8)
Number (%) of subjects with adverse events by system organ class and preferred term				
Ear and labyrinth disorders	4 (2.2)	13 (7.1)	12 (6.6)	15 (8.1)
Vertigo	4 (2.2)	13 (7.1)	12 (6.6)	15 (8.1)
Eye disorders	1 (0.5)	6 (3.3)	9 (4.9)	13 (7.0)
Vision blurred	1 (0.5)	6 (3.3)	9 (4.9)	13 (7.0)
Gastrointestinal disorders	37 (20.1)	48 (26.1)	37 (20.3)	44 (23.7)
Constipation	8 (4.3)	18 (9.8)	12 (6.6)	15 (8.1)
Diarrhoea	12 (6.5)	7 (3.8)	6 (3.3)	8 (4.3)
Dry mouth	4 (2.2)	16 (8.7)	20 (11.0)	20 (10.8)
Nausea	20 (10.9)	22 (12.0)	6 (3.3)	12 (6.5)
General disorders and administration site conditions	21 (11.4)	32 (17.4)	36 (19.8)	42 (22.6)
Fatigue	15 (8.2)	14 (7.6)	26 (14.3)	17 (9.1)
Oedema peripheral	7 (3.8)	19 (10.3)	15 (8.2)	27 (14.5)
Infections and infestations	13 (7.1)	12 (6.5)	17 (9.3)	16 (8.6)
Influenza	6 (3.3)	5 (2.7)	7 (3.8)	10 (5.4)
Nasopharyngitis	7 (3.8)	7 (3.8)	10 (5.5)	6 (3.2)
Investigations	6 (3.3)	24 (13.0)	24 (13.2)	24 (12.9)
Weight increased	6 (3.3)	24 (13.0)	24 (13.2)	24 (12.9)
Musculoskeletal and connective tissue disorders	8 (4.3)	10 (5.4)	6 (3.3)	5 (2.7)
Arthralgia	8 (4.3)	10 (5.4)	6 (3.3)	5 (2.7)
Nervous system disorders	56 (30.4)	102 (55.4)	101 (55.5)	109 (58.6)
Disturbance in attention	4 (2.2)	10 (5.4)	12 (6.6)	15 (8.1)
Dizziness	28 (15.2)	68 (37.0)	76 (41.8)	93 (50.0)
Headache	30 (16.3)	27 (14.7)	25 (13.7)	16 (8.6)
Somnolence	11 (6.0)	37 (20.1)	24 (13.2)	34 (18.3)

Subjects are only counted once per treatment for each row.
Includes data up to 999 days after last dose of study drug.
MedDRA (version 12.0) coding dictionary applied.
MedDRA = Medical Dictionary for Regulatory Activities; n = number of subjects.

The most frequently occurring treatment related AEs for pregabalin-treated subjects were dizziness, somnolence and increased weight. The most frequently occurring treatment related AEs for placebo-treated subjects were dizziness and headache. AEs considered related to treatment in at least 5% of subjects in any treatment group are summarized in Table 19.

Table 19. Summary of Treatment-Emergent Treatment Related Adverse Events

Adverse Event	Placebo	Pregabalin 300 mg/Day	Pregabalin 450 mg/Day	Pregabalin 600 mg/Day	All Pregabalin
	N=184 n (%)	N=183 n (%)	N=182 n (%)	N=186 n (%)	N=551 n (%)
Dizziness	23 (12.5)	67 (36.6)	70 (38.5)	90 (48.4)	227 (41.2)
Somnolence	10 (5.4)	36 (19.7)	23 (12.6)	33 (17.7)	92 (16.7)
Weight increased	6 (3.3)	23 (12.6)	23 (12.6)	24 (12.9)	70 (12.7)
Peripheral edema	5 (2.7)	16 (8.7)	12 (6.6)	22 (11.8)	50 (9.1)
Dry mouth	4 (2.2)	14 (7.7)	19 (10.4)	20 (10.8)	53 (9.6)
Disturbance in attention	3 (1.6)	10 (5.5)	11 (6.0)	15 (8.1)	36 (6.5)
Fatigue	10 (5.4)	11 (6.0)	26 (14.3)	14 (7.5)	51 (9.3)
Vertigo	3 (1.6)	12 (6.6)	11 (6.0)	14 (7.5)	37 (6.7)
Vision blurred	1 (0.5)	5 (2.7)	7 (3.8)	11 (5.9)	23 (4.2)
Constipation	7 (3.8)	12 (6.6)	9 (4.9)	10 (5.4)	31 (5.6)
Nausea	12 (6.5)	20 (10.9)	4 (2.2)	10 (5.4)	34 (6.2)
Headache	22 (12.0)	15 (8.2)	12 (6.6)	9 (4.8)	36 (6.5)
Somnolence by region					
EU	3 (3.1)	10 (10.8)	7 (7.7)	15 (15.6)	32 (11.8)
ROW	7 (8.1)	26 (28.9)	16 (17.6)	18 (20.0)	60 (22.1)

Events were reported in at least 5% of subjects in any of the treatment groups and are sorted by decreasing frequency in the 600 mg/day pregabalin treatment group.
The adverse events and serious adverse events were not separated out.
EU = European union; ROW = rest of the world; N = number of subjects; n = number of subjects with adverse event.

The treatment-emergent serious adverse events (SAEs) are summarized in Table 20. Eighteen subjects experienced SAEs: 4 placebo-treated subjects and 14 pregabalin-treated subjects. One SAE was considered related to treatment by the Investigator. This was an incidence of chest pain in a pregabalin 450 mg/day subject which resulted in that subject discontinuing from study treatment.

Table 20. Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term (All Causalities)

	Placebo n (%)	Pregabalin 300 mg/Day n (%)	Pregabalin 450 mg/Day n (%)	Pregabalin 600 mg/Day n (%)
Number (%) of subjects:				
Evaluable for adverse events	184	184	182	186
With adverse events	4 (2.2)	2 (1.1)	8 (4.4)	4 (2.2)
Number (%) of subjects with adverse events by:				
System Organ Class				
Blood and lymphatic system disorders	0	1 (0.5)	0	0
Anaemia	0	1 (0.5)	0	0
General disorders and administration site conditions	0	0	1 (0.5)	0
Chest pain	0	0	1 (0.5)	0
Hepatobiliary disorders	0	0	0	1 (0.5)
Cholelithiasis	0	0	0	1 (0.5)
Infections and infestations	1 (0.5)	0	2 (1.1)	2 (1.1)
Bronchopneumonia	0	0	1 (0.5)	0
Cellulitis	0	0	1 (0.5)	0
Gastroenteritis salmonella	1 (0.5)	0	0	0
Herpes zoster	0	0	0	1 (0.5)
Pneumonia	0	0	0	1 (0.5)
Injury, poisoning and procedural complications	3 (1.6)	1 (0.5)	2 (1.1)	1 (0.5)
Drug exposure during pregnancy	1 (0.5)	0	0	0
Fall	0	0	0	1 (0.5)
Head injury	1 (0.5)	0	0	0
Joint sprain	0	0	1 (0.5)	0
Muscle injury	1 (0.5)	0	0	0
Muscle strain	1 (0.5)	0	0	0
Radius fracture	0	0	1 (0.5)	0
Road traffic accident	1 (0.5)	0	0	0
Vascular injury	0	1 (0.5)	0	0
Musculoskeletal and connective tissue disorders	1 (0.5)	0	2 (1.1)	0
Arthralgia	0	0	1 (0.5)	0
Back pain	1 (0.5)	0	1 (0.5)	0
Nervous system disorders	0	0	0	1 (0.5)
Cerebrovascular accident	0	0	0	1 (0.5)
Pregnancy, puerperium and perinatal conditions	1 (0.5)	0	0	0
Abortion spontaneous	1 (0.5)	0	0	0
Renal and urinary disorders	0	0	1 (0.5)	0
Nephrolithiasis	0	0	1 (0.5)	0

Subjects were only counted once per treatment for each row.
Includes data up to 999 days after last dose of study drug.
MedDRA (version 12.0) coding dictionary applied.
MedDRA = Medical Dictionary for Regulatory Activities; n = number of subjects.

Subject Discontinuations: A total of 138 subjects withdrew from the study due to treatment-emergent AEs: 34 subjects (19%, 300 mg/day pregabalin), 36 subjects (20%, 450 mg/day pregabalin), 48 subjects (26%, 600 mg/day pregabalin) and 20 subjects (11%, placebo). The most common all causality treatment-emergent AEs leading to discontinuation in pregabalin-treated subjects were dizziness, vertigo and somnolence. The number of

subjects discontinuing with dizziness increased with pregabalin dose. Permanent discontinuations due to all causality treatment-emergent AEs are summarized in Table 21.

Table 21. Permanent Discontinuations Due to All Causality Treatment Emergent Adverse Events[a]

Number (%) of Subjects Adverse Event/ Preferred Term	Placebo N=184	Pregabalin 300 mg/Day N=183	Pregabalin 450 mg/Day N=182	Pregabalin 600 mg/Day N=186	All Pregabalin N=551
Dizziness	1 (0.5)	9 (4.9)	14 (7.7)	19 (10.2)	42 (7.6)
Somnolence	0 (0.0)	7 (3.8)	3 (1.6)	7 (3.8)	17 (3.1)
Vertigo	2 (1.1)	4 (2.2)	7 (3.8)	6 (3.2)	17 (3.1)
Nausea	0 (0.0)	6 (3.3)	0 (0.0)	5 (2.7)	11 (2.0)
Disturbance in attention	0 (0.0)	2 (1.1)	1 (0.5)	6 (3.2)	9 (1.6)
Edema peripheral	1 (0.5)	2 (1.1)	0 (0.0)	5 (2.7)	7 (1.3)
Vomiting	0 (0.0)	3 (1.6)	2 (1.1)	2 (1.1)	7 (1.3)
Weight increased	0 (0.0)	3 (1.6)	2 (1.1)	2 (1.1)	7 (1.3)
Dyspnoea	0 (0.0)	2 (1.1)	1 (0.5)	2 (1.1)	5 (0.9)
Fatigue	3 (1.6)	1 (0.5)	1 (0.5)	2 (1.1)	4 (0.7)
Dry mouth	0 (0.0)	2 (1.1)	0 (0.0)	2 (1.1)	4 (0.7)
Abdominal pain	2 (1.1)	2 (1.1)	1 (0.5)	1 (0.5)	4 (0.7)
Insomnia	0 (0.0)	2 (1.1)	2 (1.1)	0 (0.0)	4 (0.7)
Sedation	0 (0.0)	1 (0.5)	2 (1.1)	0 (0.0)	3 (0.5)
Vision blurred	0 (0.0)	2 (1.1)	1 (0.5)	0 (0.0)	3 (0.5)
Ataxia	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.1)	2 (0.4)
Balance disorder	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.1)	2 (0.4)
Fluid retention	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.1)	2 (0.4)
Arthritis	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.5)	2 (0.4)
Chest pain	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.5)	2 (0.4)
Coordination abnormal	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.5)	2 (0.4)
Dysarthria	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.5)	2 (0.4)
Feeling drunk	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.5)	2 (0.4)
Joint swelling	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.5)	2 (0.4)
Edema	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.5)	2 (0.4)
Diarrhoea	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.5)	2 (0.4)
Libido decreased	1 (0.5)	1 (0.5)	0 (0.0)	1 (0.5)	2 (0.4)
Memory impairment	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.5)	2 (0.4)
Restlessness	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.5)	2 (0.4)
Anxiety	1 (0.5)	0 (0.0)	2 (1.1)	0 (0.0)	2 (0.4)
Increased appetite	0 (0.0)	0 (0.0)	2 (1.1)	0 (0.0)	2 (0.4)
Arthralgia	0 (0.0)	1 (0.5)	1 (0.5)	0 (0.0)	2 (0.4)
Constipation	0 (0.0)	1 (0.5)	1 (0.5)	0 (0.0)	2 (0.4)
Headache	0 (0.0)	1 (0.5)	1 (0.5)	0 (0.0)	2 (0.4)
Paraesthesia	0 (0.0)	1 (0.5)	1 (0.5)	0 (0.0)	2 (0.4)
Speech disorder	0 (0.0)	1 (0.5)	1 (0.5)	0 (0.0)	2 (0.4)
Generalized edema	0 (0.0)	2 (1.1)	0 (0.0)	0 (0.0)	2 (0.4)

Events are sorted by decreasing frequency in the all pregabalin treatment group.
N = number of subjects.
a. Table shows number of subjects discontinuing with each adverse event although subjects may have discontinued with more than one adverse event.

In 29 pregabalin-treated subjects and 3 placebo-treated subjects the dose was reduced or temporarily discontinued due to all causality AEs. In 23 pregabalin and 2 placebo subjects the dose was reduced or temporarily discontinued due to treatment-related AEs.

Deaths: There were no deaths reported during the study.

Laboratory Parameters: The median changes from baseline to last observation in laboratory test parameters did not vary significantly among the treatment groups. No evidence of a relationship between study treatment and laboratory test parameters were seen from these median changes. Nineteen subjects had laboratory test abnormalities reported as AEs.

Vital Signs: Clinically significant decreases in systolic blood pressure (<90 mmHg and a decrease of 30 mmHg or more from baseline) were recorded in 3 subjects: 1 pregabalin 300 mg/day subject and 2 pregabalin 600 mg/day subjects.

Using a criterion of a ≥7% from baseline to end of treatment, weight increased significantly for 57 pregabalin-treated subjects (22 subjects [13%; 300 mg/day], 12 subjects [7%; 450 mg/day], 23 subjects [15%; 600 mg/day]), and 11 placebo-treated subjects. Weight decreased by ≥7% from baseline to end of treatment in 6 pregabalin-treated subjects (4 subjects [2%; 300 mg/day], 2 subjects [1%; 600 mg/day]), and 4 placebo-treated subjects.

At baseline, 1 placebo and 2 pregabalin 300 mg/day subjects had abnormal ECG findings considered clinically significant. Post-baseline, 1 placebo and 3 pregabalin 300 mg/day subjects, 1 pregabalin 450 mg/day subject and 1 pregabalin 600 mg/day subject had abnormal ECG findings considered clinically significant.

Neurological Examinations: The most frequent change in neurological response for all subjects was a deterioration of ankle reflexes, occurring in 3.3% of pregabalin subjects and 4.3% of placebo subjects.

CONCLUSIONS: The pregabalin 450 mg/day treatment group showed consistent efficacy across all endpoints. Consistent benefit was observed across all pregabalin doses for Sleep Disturbance. These findings are supported by the following:

- Pregabalin at 450 mg/day dose was demonstrated to reduce mean pain score compared to placebo. The reductions in pain were clinically meaningful and significant.
- Pregabalin at doses of 300, 450 and 600 mg/day demonstrated reduction in fibromyalgia pain within 1 week of initiating treatment that was sustained throughout the 14 week course of treatment for the 450 mg/day dose and up to at least Week 6 for all doses.
- Pregabalin at doses of 450 and 600 mg/day demonstrated statistically significantly greater global impression of improvement at endpoint compared with placebo treatment.
- All pregabalin doses provided improvements in subject reported sleep outcomes, as demonstrated by the improvement on the MOS Sleep subscales of Sleep Disturbance and the Sleep Quality diary.

- Pregabalin at 450 mg/day was superior compared with placebo on the FIQ total score, demonstrating functional improvements with pregabalin treatment.

- Consistent with its established safety profile, pregabalin was generally well tolerated in subjects with fibromyalgia; no new safety concerns were identified.