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

PROTOCOL NO.: A0081208

PROTOCOL TITLE: Randomized, Double-Blind, Multicenter, Placebo-Controlled Study to Evaluate Efficacy and Safety of Pregabalin (CI-1008) in the Treatment of Fibromyalgia

Study Centers: A total of 44 centers in Japan took part in the study and randomized subjects.

Study Initiation and Final Completion Dates: 17 March 2009 and 23 May 2011

Phase of Development: Phase 3

Study Objectives:

Primary Objective:

- To evaluate the efficacy of pregabalin (300 to 450 mg/day, twice daily [BID]) compared with placebo for the symptomatic relief of pain in subjects with fibromyalgia.

Secondary Objectives:

- To evaluate the safety and tolerability of pregabalin (300 to 450 mg/day, BID) in fibromyalgia subjects.
- To evaluate the efficacy of pregabalin (300 to 450 mg/day, BID) for improvement of Patient Global Impressions of Change (PGIC) and pain based on the Visual Analog Scale (VAS) in subjects with fibromyalgia.
- To evaluate the efficacy of pregabalin (300 to 450 mg/day, BID) for improvement of other domains relevant to fibromyalgia including sleep disturbance, function fibromyalgia impact questionnaire (FIQ), health-related quality of life (QOL), and mood disturbance.

METHODS

Study Design: This was a double-blind, randomized, placebo-controlled, parallel-group, multicenter study, consisting of a 1-week screening phase, a 15-week treatment phase (3-week dose optimization phase, a 12-week fixed dose treatment phase), and a 1-week taper phase. The schedule of activities are presented in Table 1.

Table 1. Schedule of Activities

Activity	Single-Blind	Double-Blind							
	Screening Phase	Treatment Phase							Taper Phase
Evaluation Term	Screening (Week -1)	Baseline (Week 0)	Week 1	Week 2	Week 3	Week 7	Week 11	Week 15/At Discontinuation	Week 16
Visit Point	V1	V2	V3	V4	V5	V6	V7	V8	V9
Allowable Days	7-14 Days Before V2[a]	-	±3	±3	±3	±3	±3	±3	+3
Informed consent	X[b]								
Inclusion/exclusion	X	X							
Subject background/medical history/complication	X								
Tender point count	X								
Physical examination	X							X	X
Edema assessment	X							X	X
Height	X								
Weight	X							X	X
Blood pressure/pulse rate	X					X		X	X
Abbreviated neurological examination and ophthalmologic assessments	X							X	X
Visual acuity and funduscopic examination[c]	X							X	
12 lead ECG[c]	X							X	
Clinical labs: pregnancy test (serum)	X					X		X	X
Clinical labs: hematology, chemistry and urinalysis	X					X		X	X
Clinical labs: glucose		X				X		X	X
Clinical labs: erythrocyte sedimentation rate at local lab	X[d]								
Concentration of drug in the plasma[e]						X		X[f]	
Telephone check[g]		←	—	—	—	—	—	→	
Daily pain/sleep[h] (pain and sleep quality)	←	—	—	—	—	—	—	→	
Patient global impression of change[i]								X	
Medical outcomes study - sleep scale		X				X		X	
Fibromyalgia impact questionnaire		X				X		X	
Short-form 36 health survey		X				X		X	
Hospital anxiety and depression scale		X						X	
Pain VAS	X	X	X	X	X	X	X	X	
Suicidal behaviors questionnaire-revised	X								
Patient health questionnaire-9	X								
Columbia-suicide severity rating scale	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X

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Evaluation Term	Screening (Week -1)	Baseline (Week 0)	Week 1	Week 2	Week 3	Week 7	Week 11	Week 15/At Discontinuation	Week 16
Visit Point	V1	V2	V3	V4	V5	V6	V7	V8	V9
Allowable Days	7-14 Days Before V2[a]	-	±3	±3	±3	±3	±3	±3	+3
Compliance			X	X	X	X	X	X	X
Adverse events			X	X	X	X	X	X	X
Serious adverse events[i]	←	—	—	—	—	—	—	—	→
The sample banking for exploratory research[j]		←	—	—	—	—	—	—	→

ECG = electrocardiogram; V = visit; VAS = visual analog scale.

a. In the cases exceeding 14 days because of tests such as funduscopic examination, a maximum of 21 days was allowed.
b. Informed consent was obtained prior to the screening for all subjects who need a washout period for prohibited medications prior to this visit.
c. The following assessments were performed at Baseline (from V1 to V2) and the end of treatment phase (from V8 to V9): visual acuity, funduscopic examination and 12-lead ECG.
d. Erythrocyte Sedimentation Rate test was performed at each study site.
e. The time of last dosing prior to Pharmacokinetic sampling was accurately recorded.
f. Not performed at discontinuation.
g. Subjects were called at least once during each visit interval between V2 and V8 in order to confirm if their pains and sleep disturbance are properly evaluated/entered in the daily pain diary.
h. Self-assessment was performed daily at awakening.
i. Reporting period: from the consent acquisition to the 28th day after the final dosing.
j. Blood collection for sample banking was performed once during the period from V2 to V9 in the subjects who agreed to participate in this additional research activity.

Number of Subjects (Planned and Analyzed): The study was planned to enroll 498 subjects (249 subjects each in the placebo and pregabalin groups). A total of 501 subjects were randomized to either treatment group in Japan, and 498 subjects were treated (248 with placebo, 250 with pregabalin).

Diagnosis and Main Criteria for Inclusion: Males or female subjects, ≤18 years of age who met the American College of Rheumatology criteria for fibromyalgia at the start of Screening (Visit 1), had a score of ≥40 mm on the Pain VAS at Screening and Baseline, and had assessed and documented their pain during the last 4 of 7 days in pain diaries by Visit 2, with an average pain score of ≥4.

Subjects were excluded if their pain decreased by ≥30% on the Pain VAS at randomization (Visit 2) compared to Screening (Visit 1), or if pain was potentially affecting assessment or self-evaluation of fibromyalgia; subjects with depression requiring antidepressant therapy; subjects with risk of suicide or self-harm as determined by the Investigator; subjects with active malignancy or a history of malignancy; subjects with creatinine clearance ≤60 mL/min as estimated from serum creatinine using the Cockcroft-Gault formula; and subjects unsuitable for inclusion in the study in the judgment of the Investigators.

Study Treatment: In the 15-week double-blind treatment phase (3-week dose optimization phase, 12-week fixed dose treatment phase), pregabalin at doses ranging from 150 to 450 mg/day (using capsules containing 75 or 150 mg pregabalin) or matching placebo was administered twice a day: morning and evening, before or after meals.

Treatment was started at 150 mg/day (75 mg on the evening of Visit 2), and the dose was increased to 300 mg/day 1 week later (Visit 3). Treatment was discontinued if there were any safety problems at 150 mg/day or 300 mg/day. Based on the efficacy and safety in individual subjects, the dose was then increased to 450 mg/day starting at Week 2 (Visit 4). Treatment was discontinued if there were any safety problems at 300 mg/day. The dose could be adjusted until Visit 5 (dose optimization phase), but was not to be changed subsequently (ie, fixed dose treatment phase).

The following medications were permitted for additional pain relief: Acetaminophen, and nonsteroidal anti-inflammatory drugs (including cyclooxygenase-2 inhibitor or COXIBs); and in the case of the latter medication, subjects must have been on a stable regimen longer than 30 days.

Efficacy Endpoints:

Primary Endpoint:

- Endpoint mean pain score (the mean value of pain scores in the pain diary was assessed by an 11-point numeric rating scale, ranging from 0 to 10, for the last 7 days including the endpoint assessment)

Secondary Endpoint:

- Patient Global Impression of Change (PGIC)
- Medical Outcomes Study - Sleep Scale (MOS-Sleep Scale)
- Quality of sleep score (the mean value of scores in a diary to be assessed by an 11-point numeric rating scale ranging from 0 to 10 for the last 7 days)
- Japanese version of FIQ
- Short-Form 36 Health Survey (SF-36)
- Pain Visual Analog Scale (VAS)
- Hospital Anxiety and Depression Scale (HADS)

Safety Evaluations: Adverse events (AEs), serious adverse events (SAEs), body weight, blood pressure, pulse rate, physical examinations, edema assessment, neurological examinations and ophthalmologic examinations, 12-lead electrocardiogram (ECG), clinical laboratory testing (hematology, serum chemistry, urinalysis), and Columbia-Suicide Severity Rating Scale (C-SSRS).

Statistical Methods:

Full Analysis Set (FAS): The FAS consisted of all randomized subjects who received at least 1 dose of study medication, regardless of compliance with study medication, and had at least 1 pain score on study medication.

Per Protocol Analysis Set (PPS): The PPS consists of all subjects without major protocol deviations in the FAS.

The safety analysis set consisted of all subjects who have taken at least 1 dose of study medication.

The primary analysis was the comparison between the pregabalin group (fixed doses of 300 or 450 mg/day) and placebo group, based on an analysis of covariance model, including dose groups and baseline mean pain score as factor. A 1-sided test with a significant level of 0.025 was used for the comparison.

The mean pain score was also calculated each week in the treatment phase and analyzed as the time-course measurement data. The mixed effect model taking baseline value as covariance was used for the analysis, which included subjects as the random effect and dose groups, points at time of evaluation, and interaction between a dose group and its point at time of evalution as the fixed effects.

The secondary endpoints PGIC, QOL, SF-36, FIQ, MOS-Sleep Scale, Quality of Sleep Scale, HADS and Pain VAS score were evaluated using descriptive statistics as appropriate.

Pharmacokinetic (PK) analysis: Population PK analysis was performed to assess the PK of pregabalin.

Safety Analysis: AEs, weight, blood pressure, pulse rate, physical examinations, ECG and clinical laboratory testing were summarized descriptively by treatment group. The results of physical examination, edema assessment, neurological examinations and ophthalmologic examinations, 12-lead ECGs, laboratory tests (hematology, blood biochemistry, urinalysis), and C-SSRS were summarized. Tables of the laboratory tests were prepared to elucidate clinically significant abnormalities. The C-SSRS is mapped to the Columbia–Classification Algorithm of Suicide Assessment categories.

Interim analysis: An interim analysis of the first 324 and 400 subjects was planned, in order to stop the study early if greater-than-expected efficacy could be confirmed or if the expected efficacy could not be confirmed. The criteria for stopping the study were based on the O'Brien-Fleming type alpha spending function of Lan and DeMets (1983).

RESULTS

Subject Disposition and Demography: In this study, 501 subjects were randomized to either treatment group. Of the 498 treated subjects, 248 received placebo and 250 pregabalin (Table 2). Three of the randomized subjects were withdrawn without receiving any study medication because of conflict with the inclusion/exclusion criteria or withdrawal of consent.

Of the 498 treated subjects, 40 in the placebo group and 43 in the pregabalin group withdrew from the study. The most common reasons were inadequate response in the placebo group (26 subjects) and AEs in the pregabalin group (24 subjects). Six subjects in the placebo group and 19 in the pregabalin group withdrew from the study because of treatment-related AEs (Table 2).

Table 2. Subject Disposition

	Placebo	Pregabalin
Assigned to study treatment	250	251
Treated	248	250
Completed	208 (83.2)	207 (82.5)
Discontinued	40 (16.0)	43 (17.1)
Reason of discontinuation[a]		
Related to study drug	32 (12.9)	29 (11.6)
Adverse event	6 (2.4)	19 (7.6)
Insufficient clinical response	26 (10.5)	10 (4.0)
Not related to study drug	8 (3.2)	14 (5.6)
Adverse event	2 (0.8)	5 (2.0)
Does not meet entrance criteria	2 (0.8)	5 (2.0)
Lost to follow up	0	1 (0.4)
Other[b]	2 (0.8)	2 (0.8)
Protocol violation	0	1 (0.4)
No longer willing to participate in study	2 (0.8)	0
Analyzed for efficacy		
FAS	248 (99.2)	250 (99.6)
PPS	232 (92.8)	231 (92.0)
Analyzed for safety		
Adverse events	248 (99.2)	250 (99.6)
Laboratory data	246 (98.4)	250 (99.6)

FAS = full analysis set; PPS = per protocol set.

a. The percentages in the numbers of subjects by reason for discontinuation are the percentages relative to the number of treated subjects.

b. Family obligations in 1 subject and failure to visit because a scheduled visit could not be rescheduled for 1 subject (both in placebo group), and treatment noncompliance in 1 subject and discontinued treatment because of dental treatment in 1 subject (both in pregabalin group).

The subject demographic characteristics are presented in Table 3. The gender composition in the safety analysis set showed that there were more females, with 31 males (12.5%) and 217 females (87.5%) in the placebo group, and 24 males (9.6%) and 226 females (90.4%) in the pregabalin group. The mean age (range) was 46.7 years (19 to 78 years) in the placebo group, and 47.9 years (19 to 80 years) in the pregabalin group. There were 21 subjects 65 years of age or older in the placebo group (8.5%) and 24 subjects in the pregabalin group (9.6%). There was no apparent bias in the subject demographics between the 2 groups.

Mean duration for fibromyalgia was 62.0 months (range from 0.3 to 508.8 months) in placebo group and 69.6 months (range from 0.3 to 505.1 months) in pregabalin group, and that was comparable in both groups. Mean pain score at Baseline was 6.4 (range from 3.7 to 10.0) in placebo group, 6.5 (range from 4.0 to 10.0) in pregabalin group, and was well-balanced in both groups.

Table 3. Demographic Characteristics

Characteristics	Placebo			Pregabalin			Total		
	Male N=31	Female N=217	Total N=248	Male N=24	Female N=226	Total N=250	Male N=55	Female N=443	Total N=498
Hormonal status									
Premenopausal	-	133 (61.3)	-	-	140 (61.9)	-	-	273 (61.6)	-
Postmenopausal	-	84 (38.7)	-	-	86 (38.1)	-	-	170 (38.4)	-
Age (years)									
<18	0	0	0	0	0	0	0	0	0
18-44	18 (58.1)	86 (39.6)	104 (41.9)	16 (66.7)	85 (37.6)	101 (40.4)	34 (61.8)	171 (38.6)	205 (41.2)
45-64	10 (32.3)	113 (52.1)	123 (49.6)	5 (20.8)	120 (53.1)	125 (50.0)	15 (27.3)	233 (52.6)	248 (49.8)
≥65	3 (9.7)	18 (8.3)	21 (8.5)	3 (12.5)	21 (9.3)	24 (9.6)	6 (10.9)	39 (8.8)	45 (9.0)
Mean	43.5	47.2	46.7	45.1	48.3	47.9	44.2	47.7	47.3
SD	12.9	12.5	12.6	14.4	11.7	12	13.5	12.1	12.3
Range	23-76	19-78	19-78	23-78	19-80	19-80	23-78	19-80	19-80
Race									
Asian	31 (100.0)	217 (100.0)	248 (100.0)	24 (100.0)	226 (100.0)	250 (100.0)	55 (100.0)	443 (100.0)	498 (100.0)
Weight (kg)									
Mean	63.3	55.1	56.2	68.2	54.2	55.5	65.4	54.6	55.8
SD	10	8.4	9	12.7	9.9	11	11.4	9.2	10
Range	47.0-90.9	38.9-82.4	38.9-90.9	53.0-93.1	37.2-104.8	37.2-104.8	47.0-93.1	37.2-104.8	37.2-104.8
N	31 (100.0)	217 (100.0)	248 (100.0)	24 (100.0)	226 (100.0)	250 (100.0)	55 (100.0)	443 (100.0)	498 (100.0)
Height (cm)									
Mean	167.8	157.2	158.5	167.8	157.3	158.3	167.8	157.2	158.4
SD	5.1	5.9	6.8	5.8	5.6	6.4	5.4	5.7	6.6
Range	159.0-179.6	131.9-173.4	131.9-179.6	157.6-176.0	143.8-170.0	143.8-176.0	157.6-179.6	131.9-173.4	131.9-179.6
N	31 (100.0)	217 (100.0)	248 (100.0)	24 (100.0)	226 (100.0)	250 (100.0)	55 (100.0)	443 (100.0)	498 (100.0)

BMI is defined as weight/(height×.01)×2.
BMI = body mass index; N = number of subjects; SD = standard deviation.

Efficacy and Pharmacokinetic Results: As a result of interim analysis of the data from 327 subjects, the independent data monitoring committee allowed the study to continue as planned.

Primary Endpoint Results: The change in the mean pain score at the final assessment in the pregabalin group was greater than that in the placebo group (difference versus [vs] placebo: -0.44), and the difference was statistically significant (p=0.0046). The results for the PPS were the same as for the FAS (Table 4).

Table 4. Mean Pain Score (FAS, Last Observation Carried Forward)

	Placebo (N=248)				Pregabalin (N=250)				
	LS	SE	95% CI		LS	SE	95% CI		p-Value
			Lower	Upper			Lower	Upper	
Mean	5.45	0.12	5.21	5.68	5.01	0.12	4.77	5.24	
Change	-1.03	0.12	-1.27	-0.80	-1.48	0.12	-1.71	-1.24	
Difference from placebo[a]					-0.44	0.17	-0.78	-0.11	0.0046[b]

ANCOVA = analysis of covariance; CI = confidence interval; FAS = full analysis set; LS = least square; SE = standard error.

a. ANCOVA using treatment group as factor and baseline value as covariate.
b. Statistically significant (significance level 0.0253 for one sided test based on O'Brien-Fleming type alpha spending function of Lan and DeMets).

Secondary Endpoints Results:

Patient Global Impression of Change: Pregabalin group showed statistically significantly greater improvement compared to the placebo group based on modified ridit chi-square test for the 7 scales of PGIC (p=0.0078), suggesting improvement of subjects' pain condition associated with fibromyalgia (Table 5).

Table 5. Patient Global Impression of Change (PGIC)

	Placebo (N=248)	Pregabalin (N=250)
Number assessed[a]	247 (99.6)	249 (99.6)
Any improvement	154 (62.1)	175 (70.0)
Very much improved	16 (6.5)	31 (12.4)
Much improved	50 (20.2)	65 (26.0)
Minimally improved	88 (35.5)	79 (31.6)
No change	60 (24.2)	43 (17.2)
Any worsening	33 (13.3)	31 (12.4)
Minimally worse	14 (5.6)	14 (5.6)
Much worse	13 (5.2)	13 (5.2)
Very much worse	6 (2.4)	4 (1.6)
Comparison of pregabalin treatment group to placebo[b]		
p-Value	0.0078*	

* Statistically significant at 0.05 level.
PGIC is scaled from 1 to 7: 1= very much improved, 2= much improved, etc, 7= very much worse.
'Any improvement' includes 1, 2, and 3, 'Any worsening' includes 4, 5, and 6.
N = number of subjects; PGIC = patient global impression of change.
a. Numbers of subjects with available data for this analysis.
b. Based on chi-square test with a modified rigid transformation.

Medical Outcomes Study - Sleep Scale (MOS-Sleep Scale): Improvement in sleep disturbance ($p < 0.0001$), awakening short of breath or with headache ($p = 0.0049$), quantity of sleep ($p = 0.0007$), sleep adequacy ($p < 0.0001$), and overall sleep problems ($p = 0.0137$) was significantly better on pregabalin than on placebo (Table 6).

Table 6. Medical Outcomes Study Sleep Scale Scores

Statistic[a]	Placebo (N=248)					Pregabalin (N=250)					p-Value
	N	Least Squares	SE	95% CI Lower	95% CI Upper	N	Least Squares	SE	95% CI Lower	95% CI Upper	
Sleep disturbance											
Mean	247	39.76	1.31	37.18	42.33	249	30.27	1.31	27.71	32.84	
Mean change		-8.13	1.31	-10.71	-5.56		-17.62	1.31	-20.18	-15.05	
Difference from placebo							-9.48	1.85	-13.12	-5.85	<0.0001*
Snoring											
Mean	247	24.19	1.33	21.58	26.81	249	29.17	1.33	26.57	31.78	
Mean change		-1.61	1.33	-4.23	1		3.37	1.33	0.76	5.97	
Difference from placebo							4.98	1.88	1.29	8.68	0.9958
Awaken short of breath											
Mean	247	22.99	1.36	20.31	25.67	249	18	1.36	15.33	20.67	
Mean change		-3.02	1.36	-5.7	-0.34		-8.01	1.36	-10.68	-5.34	
Difference from placebo							-4.99	1.92	-8.77	-1.21	0.0049*
Quantity of sleep											
Mean	247	5.7	0.06	5.57	5.82	249	5.99	0.06	5.86	6.12	
Mean change		0.17	0.06	0.04	0.29		0.46	0.06	0.33	0.59	
Difference from placebo							0.29	0.09	0.11	0.47	0.0007*
Sleep adequacy											
Mean	247	36.91	1.41	34.15	39.68	249	44.39	1.4	41.64	47.14	
Mean change		8.02	1.41	5.26	10.78		15.5	1.4	12.74	18.25	
Difference from placebo							7.48	1.99	3.58	11.38	<0.0001*
Somnolence											
Mean	247	36.41	1.29	33.88	38.93	249	47.71	1.28	45.2	50.23	
Mean change		-4.66	1.29	-7.18	-2.13		6.65	1.28	4.14	9.17	
Difference from placebo							11.31	1.82	7.74	14.87	1
Overall sleep problems index											
Mean	247	42.66	0.96	40.78	44.54	249	39.67	0.95	37.79	41.54	
Mean change		-7.07	0.96	-8.95	-5.19		-10.06	0.95	-11.93	-8.18	
Difference from placebo							-2.99	1.35	-5.65	-0.33	0.0137*

* Statistically significant at 0.025 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; SE = standard error.
a. Based on the results of ANCOVA model (including effects for treatments, and the baseline value as covariate).

Quality of Sleep Score: The mean change in quality of sleep score was also significantly better at any time points from Week 1 through Week 15 in the pregabalin group compared to the placebo group (p≤0.0001) (Table 7).

Table 7. Mean Sleep Quality Scores

Statistic[a]	Placebo (N=248)				Pregabalin (N=250)				p-Value
	Least Squares	SE	95% CI		Least Squares	SE	95% CI		
			Lower	Upper			Lower	Upper	
Mean	4.91	0.12	4.67	5.14	4.17	0.12	3.94	4.41	
Mean change	-0.79	0.12	-1.02	-0.56	-1.52	0.12	-1.75	-1.29	
Difference from placebo					-0.73	0.17	-1.06	-0.40	<0.0001*

* Statistically significant at 0.025 level.
Endpoint mean sleep quality score is defined as the mean of the last 7 daily sleep diary ratings while taking the study medication, up to and including day after last dose.
Scores range from 0-10 with higher scores indicating decreased sleep.
ANCOVA = analysis of covariance; CI = confidence interval; N = number of subjects; SE = standard error.
a. Based on the results of ANCOVA model (including effects for treatment, and the baseline score value as covariate).

Fibromyalgia Impact Questionnaire (FIQ; Japanese version): The total score of FIQ was statistically significantly better in the pregabalin group compared to the placebo group (Table 8).

Table 8. Fibromyalgia Impact Questionnaire (FIQ) Total Scores

Statistic[a]	Placebo (N=248)				Pregabalin (N=250)				p-Value
	Least Squares	SE	95% CI		Least Squares	SE	95% CI		
			Lower	Upper			Lower	Upper	
Mean	44.89	1.08	42.77	47.00	41.56	1.07	39.45	43.66	
Mean change	-7.26	1.08	-9.38	-5.15	-10.59	1.07	-12.70	-8.49	
Difference from placebo					-3.33	1.52	-6.31	-0.35	0.0144*

* Statistically significant at 0.025 level.
Scores range from 0 to 100 with higher scores indicating more impairment.
ANCOVA = analysis of covariance; CI = confidence interval; N = number of subjects; SE = standard error.
a. Based on the results of ANCOVA model (including effects for treatment, and the baseline score value as covariate).

As assessed by the FIQ subscores feel good (p=0.0052), pain (p=0.0238), fatigue (p=0.0075), and morning tiredness (p=0.0023), the pregabalin group was statistically significantly better compared to the placebo group (Table 9).

Table 9. Analysis of Fibromyalgia Impact Questionnaire (FIQ) Subscores

Statistic[a]	Placebo (N=248)				Pregabalin (N=250)				p-Value
	Least Squares	SE	95% CI Lower	95% CI Upper	Least Squares	SE	95% CI Lower	95% CI Upper	
Physical Function									
Mean	3.03	0.11	2.81	3.25	2.74	0.11	2.53	2.96	
Mean change	-0.19	0.11	-0.41	0.03	-0.47	0.11	-0.69	-0.25	
Difference from placebo					-0.28	0.16	-0.59	0.03	0.0376
Feel Good									
Mean	5.94	0.17	5.59	6.28	5.3	0.17	4.96	5.64	
Mean change	-0.82	0.17	-1.16	-0.47	-1.45	0.17	-1.79	-1.11	
Difference from placebo					-0.63	0.25	-1.12	-0.15	0.0052*
Work Miss									
Mean	1.89	0.15	1.6	2.18	1.87	0.15	1.58	2.16	
Mean change	-0.3	0.15	-0.59	-0.01	-0.31	0.15	-0.6	-0.02	
Difference from placebo					-0.01	0.21	-0.42	0.4	0.4768
Housework									
Mean	4.61	0.15	4.31	4.91	4.3	0.15	4	4.6	
Mean change	-1	0.15	-1.3	-0.7	-1.32	0.15	-1.61	-1.02	
Difference from placebo					-0.31	0.21	-0.74	0.11	0.0729
Pain									
Mean	5.36	0.15	5.07	5.64	4.95	0.15	4.66	5.23	
Mean change	-1.06	0.15	-1.34	-0.77	-1.46	0.15	-1.75	-1.18	
Difference from placebo					-0.41	0.21	-0.81	0	0.0238*
Tiredness									
Mean	5.94	0.14	5.66	6.22	5.45	0.14	5.17	5.73	
Mean change	-0.94	0.14	-1.22	-0.66	-1.43	0.14	-1.71	-1.15	
Difference from placebo					-0.49	0.2	-0.89	-0.1	0.0075*
Morning									
Mean	5.73	0.15	5.44	6.02	5.13	0.15	4.84	5.42	
Mean change	-0.97	0.15	-1.26	-0.68	-1.56	0.15	-1.85	-1.27	
Difference from placebo					-0.59	0.21	-1.01	-0.18	0.0023*
Stiffness									
Mean	5.05	0.15	4.74	5.35	4.9	0.15	4.6	5.21	
Mean change	-0.9	0.15	-1.21	-0.6	-1.05	0.15	-1.35	-0.74	
Difference from placebo					-0.14	0.22	-0.57	0.29	0.2568
Anxious									
Mean	3.92	0.16	3.61	4.23	3.64	0.16	3.33	3.94	
Mean change	-0.64	0.16	-0.95	-0.34	-0.92	0.16	-1.23	-0.62	
Difference from placebo					-0.28	0.22	-0.72	0.15	0.1011
Depression									
Mean	3.38	0.14	3.1	3.66	3.34	0.14	3.06	3.62	
Mean change	-0.51	0.14	-0.79	-0.23	-0.55	0.14	-0.83	-0.27	
Difference from placebo					-0.04	0.2	-0.44	0.35	0.4165

* Statistically significant at 0.025 level.
Scores range from 0 to 10 with higher scores indicating more impairment.
ANCOVA = analysis of covariance; CI = confidence interval; N = number of subjects; SE = standard error.
a. Based on the results of ANCOVA model (including effects for treatment, and the baseline score value as covariate).

Short-Form 36 Health Survey: SF-36 revealed statistically significantly better physical functioning and vitality in the pregabalin group versus the placebo group (Table 10).

Table 10. Analysis of SF-36 Health Survey Results

Statistic[a]	Placebo (N=248)				Pregabalin (N=250)				p-Value
	Least Squares	SE	95% CI Lower	95% CI Upper	Least Squares	SE	95% CI Lower	95% CI Upper	
Physical Functioning									
Mean	68.44	0.93	66.6	70.27	72.73	0.93	70.89	74.56	
Mean change	4.72	0.93	2.89	6.56	9.01	0.93	7.18	10.84	
Difference from placebo					4.29	1.32	1.7	6.88	0.0006*
Role Limitations-Physical									
Mean	60.9	1.3	58.34	63.46	62.58	1.3	60.03	65.13	
Mean change	8.36	1.3	5.81	10.92	10.04	1.3	7.49	12.59	
Difference from placebo					1.68	1.84	-1.93	5.29	0.1805
Bodily Pain									
Mean	43.27	1.06	41.18	45.36	45.42	1.06	43.33	47.5	
Mean change	9.5	1.06	7.41	11.59	11.65	1.06	9.56	13.73	
Difference from placebo					2.15	1.5	-0.81	5.1	0.077
General Health Perception									
Mean	44.82	0.85	43.14	46.5	46.65	0.85	44.98	48.32	
Mean change	2.83	0.85	1.16	4.51	4.66	0.85	2.99	6.33	
Difference from placebo					1.83	1.2	-0.54	4.19	0.0648
Social Functioning									
Mean	68.51	1.38	65.8	71.21	70.1	1.37	67.4	72.79	
Mean change	6.84	1.38	4.13	9.54	8.43	1.37	5.73	11.13	
Difference from placebo					1.59	1.94	-2.23	5.41	0.2068
Role Limitations-Emotional									
Mean	72.99	1.36	70.33	75.66	72.76	1.35	70.1	75.42	
Mean change	3.5	1.36	0.84	6.16	3.27	1.35	0.61	5.93	
Difference from placebo					-0.23	1.92	-4	3.54	0.548
Vitality									
Mean	42.01	1.22	39.62	44.4	46.43	1.21	44.05	48.81	
Mean change	5.12	1.22	2.72	7.51	9.53	1.21	7.15	11.92	
Difference from placebo					4.42	1.72	1.04	7.8	0.0052*
Mental Health									
Mean	64.47	0.98	62.54	66.4	67.11	0.98	65.19	69.04	
Mean change	3.33	0.98	1.4	5.26	5.97	0.98	4.05	7.9	
Difference from placebo					2.64	1.39	-0.08	5.37	0.0287

* Statistically significant at 0.025 level.
Ranges: 0 to 100, where higher scores indicate better subject status.
ANCOVA = analysis of covariance; CI = confidence interval; N = number of subjects; SE = standard error; SF = short form.
a. Based on the results of ANCOVA model (including effects for treatment, and the baseline score value as covariate).

Pain Visual Analog Scale: From Week 1 to Week 15, there was a statistically significant reduction in Pain VAS score in the pregabalin group compared to the placebo group (Table 11).

Table 11. Mean Pain VAS Scores

Statistic[a]	Placebo (N=248)				Pregabalin (N=250)				p-Value
	Least Squares	SE	95% CI Lower	95% CI Upper	Least Squares	SE	95% CI Lower	95% CI Upper	
Mean	53.61	1.45	50.77	56.45	47.42	1.44	44.59	50.24	
Mean change	-14.11	1.45	-16.95	-11.27	-20.30	1.44	-23.13	-17.48	
Difference from placebo					-6.19	2.04	-10.20	-2.18	0.0013*

* Statistically significant at 0.025 level.
Pain VAS scores range from 0-100 with higher scores indicating increased pain.
ANCOVA = analysis of covariance; CI = confidence interval; N = number of subjects; SE = standard error.
a. Based on the results of ANCOVA model (including effects for treatment, and the baseline score value as covariate).

Hospital Anxiety and Depression Scale: Although there was a pattern of improvement in anxiety on the HADS in the pregabalin group compared to the placebo group, there were no statistically significant differences in either anxiety or depression between the placebo and pregabalin groups (Table 12).

Table 12. Analysis of Hospital Anxiety and Depression Scale Scores

Statistic[a]	Placebo (N=248)					Pregabalin (N=250)					p-Value
	n	Least Squares	SE	95% CI Lower	95% CI Upper	n	Least Squares	SE	95% CI Lower	95% CI Upper	
HADS anxiety total											
Mean	247	5.77	0.18	5.42	6.11	249	5.29	0.18	4.94	5.63	
Mean change		-0.09	0.18	-0.43	0.26		-0.57	0.18	-0.92	-0.23	
Difference from placebo							-0.48	0.25	-0.97	0.01	0.0262
HADS depression total											
Mean	247	5.99	0.2	5.6	6.38	249	5.71	0.2	5.32	6.09	
Mean change		0	0.2	-0.39	0.38		-0.29	0.2	-0.67	0.1	
Difference from placebo							-0.28	0.28	-0.83	0.27	0.1561

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; n = number of subjects with a characteristic; SE = standard error.
a. Based on the results of ANCOVA model (including effects for treatment, and the baseline score value as covariate).

Safety Results: The overview of AEs is presented in Table 13. The incidence of all-causality AEs was higher in the pregabalin group (225 of 250 subjects, or 90.0%) than in the placebo group (175 of 248 subjects, or 70.6%). The incidence of treatment-related AEs was higher in the pregabalin group (82.4%) compared to the placebo group (51.6%).

Table 13. Summary of Adverse Events

	All-Causality		Treatment-Related	
	Placebo	Pregabalin	Placebo	Pregabalin
Subjects evaluable for adverse events	248	250	248	250
Number of adverse events	407	736	220	499
Subjects with				
Adverse events	175 (70.6)	225 (90.0)	128 (51.6)	206 (82.4)
Serious adverse events[a]	1 (0.4)	3 (1.2)	0	0
Severe adverse events	0	2 (0.8)	0	0
Discontinuations due to adverse events	9 (3.6)	24 (9.6)	7 (2.8)	19 (7.6)
Dose reductions/temporary discontinuations due to adverse events	11 (4.4)	30 (12.0)	7 (2.8)	28 (11.2)

a. The number of subjects with serious adverse events was based on information in the safety database.
Number of cases (%)

The treatment-emergent non-serious AEs occurring in ≥5% subjects in the pregabalin treatment group are presented in Table 14.

Table 14. Treatment-Emergent Non-Serious Adverse Events (All Causalities, ≥5 % Subjects on Pregabalin)

System Organ Class Preferred Term	Placebo n (%)	Pregabalin n (%)
Number (%) of subjects		
Evaluable for adverse events	248	250
With adverse events	113 (45.6)	195 (78.0)
Eye disorders	3 (1.2)	13 (5.2)
Vision blurred	3 (1.2)	13 (5.2)
Gastrointestinal disorders	17 (6.9)	36 (14.4)
Constipation	17 (6.9)	36 (14.4)
General disorders and administration site conditions	6 (2.4)	36 (14.4)
Feeling abnormal	3 (1.2)	20 (8.0)
Oedema peripheral	3 (1.2)	18 (7.2)
Infections and infestations	45 (18.1)	45 (18.0)
Nasopharyngitis	45 (18.1)	45 (18.0)
Investigations	9 (3.6)	39 (15.6)
Weight increased	9 (3.6)	39 (15.6)
Nervous system disorders	67 (27.0)	154 (61.6)
Dizziness	15 (6.0)	74 (29.6)
Headache	15 (6.0)	15 (6.0)
Somnolence	45 (18.1)	116 (46.4)

Subjects are only counted once per treatment for each row.
MedDRA (version 14.0) coding dictionary applied.
MedDRA = Medical Dictionary for Regulatory Activities; n = number of subjects with adverse events.

The treatment-emergent treatment-related AEs in ≥1% subjects in at least 1 treatment group are presented in Table 15.

Table 15. Treatment-Related Treatment-Emergent Adverse Events (≥1% Subjects in at Least 1 Treatment Group)

System Organ Class Preferred Term	Placebo (N=248) n (%)	Pregabalin (N=250) n (%)
Cardiac disorders	2 (0.8)	3 (1.2)
Palpitations	2 (0.8)	3 (1.2)
Ear and labyrinth disorders	2 (0.8)	10 (4.0)
Vertigo	2 (0.8)	8 (3.2)
Eye disorders	7 (2.8)	23 (9.2)
Dry eye	0	4 (1.6)
Vision blurred	2 (0.8)	13 (5.2)
Visual acuity reduced	2 (0.8)	3 (1.2)
Gastrointestinal disorders	45 (18.1)	57 (22.8)
Abdominal pain upper	4 (1.6)	4 (1.6)
Constipation	16 (6.5)	32 (12.8)
Diarrhoea	6 (2.4)	5 (2.0)
Dry mouth	2 (0.8)	6 (2.4)
Gastritis	7 (2.8)	2 (0.8)
Nausea	9 (3.6)	8 (3.2)
Stomatitis	1 (0.4)	5 (2.0)
Vomiting	3 (1.2)	3 (1.2)
General disorders and administration site conditions	14 (5.6)	44 (17.6)
Feeling abnormal	3 (1.2)	19 (7.6)
Oedema	0	3 (1.2)
Oedema peripheral	3 (1.2)	17 (6.8)
Thirst	4 (1.6)	6 (2.4)
Investigations	24 (9.7)	55 (22.0)
Alanine aminotransferase increased	0	4 (1.6)
Aspartate aminotransferase increased	0	4 (1.6)
Blood creatine phosphokinase increased	0	6 (2.4)
Blood urine present	5 (2.0)	3 (1.2)
Neutrophil count decreased	4 (1.6)	3 (1.2)
Weight decreased	3 (1.2)	0
Weight increased	7 (2.8)	36 (14.4)
White blood cell count decreased	0	3 (1.2)
Metabolism and nutrition disorders	1 (0.4)	10 (4.0)
Increased appetite	1 (0.4)	9 (3.6)
Nervous system disorders	65 (26.2)	153 (61.2)
Disturbance in attention	0	4 (1.6)
Dizziness	14 (5.6)	72 (28.8)
Headache	11 (4.4)	12 (4.8)
Somnolence	44 (17.7)	113 (45.2)
Psychiatric disorders	2 (0.8)	11 (4.4)
Euphoric mood	0	3 (1.2)
Skin and subcutaneous tissue disorders	17 (6.9)	14 (5.6)
Eczema	4 (1.6)	4 (1.6)
Pruritus	4 (1.6)	0
Rash	4 (1.6)	3 (1.2)
Total preferred term events	220	499

Subjects are counted only once per treatment in each row. For the TESS algorithm any missing severities were imputed as severe unless the subject experienced another occurrence of the same event in a given treatment for which severity was recorded.
Medical Dictionary for Regulatory Activities (version 14.0) coding dictionary applied.
N = number of subjects evaluable for adverse events; n = number of subjects with adverse events.

All-causality SAEs occurred in 5 subjects: 1 subject (liver function test abnormal) in the placebo group, 3 subjects (breast cancer, gastroenteritis viral, and musculoskeletal stiffness in 1 subject each) in the pregabalin group, and 1 subject (nephrotic syndrome) that was not treated with the study drug. The causal relations to the study drug were ruled out by Investigators in all of these events.

No deaths were reported during this study.

The Screening of C-SSRS mapped to the Columbia-Algorithm of Suicide Assessment categories is presented in Table 16. From C-SSRS assessment, there were 2 subjects with suicidal ideation reported as an AE after study drug treatment. Both subjects were reported to have suicidal ideation at Screening. The cause of suicidal ideation were considered by Investigators to be related to independent matters that temporarily occurred like work, physical deconditioning due to primary disease, or stress in everyday life for 1 subject, and family issue for the other subject.

Table 16. Screening of Columbia-Suicide Severity Rating Scale Mapped to the Columbia-Algorithm of Suicide Assessment Categories

	Placebo (N=248)	Pregabalin (N=250)
	n (%)	n (%)
Number assessed	248	250
Suicidal behavior	0	1 (0.4)
Suicide attempt <2>	0	1 (0.4)
Preparatory acts toward imminent suicidal behavior <3>	0	0
Suicidal ideation <4>	5 (2.0)	6 (2.4)
Suicidal behavior and/or ideation	5 (2.0)	7 (2.8)
Self injurious behavior, no suicidal intent <7>	0	0
No suicidal intent	243 (98.0)	243 (97.2)

< > indicates C-CASA Event Code.
N = number of subjects evaluable for AEs; n = number of subjects with characteristic.

CONCLUSIONS: This study was conducted to assess the efficacy and safety of pregabalin 300 mg/day BID or 450 mg/day (BID) in 498 subjects with fibromyalgia.

There was a statistically significant greater change in mean pain score at final assessment (primary endpoint) in the pregabalin group compared to placebo. The change in weekly pain score and the percentage of responders (FAS) were statistically significantly greater in the pregabalin group compared to the placebo group, which supported the pain relief effect of pregabalin (primary endpoint). The PGIC, FIQ total score, MOS-Sleep Scale, and quality of sleep score at final assessment were also statistically significantly better in the pregabalin group compared to the placebo group. Assessment of QOL based on the SF-36 revealed statistically significantly better physical functioning and vitality in the pregabalin group compared to the placebo group. The above results indicated that treatment with pregabalin 300 mg/day (BID) or 450 mg/day (BID) was effective.

The most common all-causality AEs in the pregabalin group were somnolence, dizziness, nasopharyngitis, weight increased and constipation. The most common AEs in the placebo group were nasopharyngitis and somnolence. The incidence of AEs was higher in the

pregabalin group (90.0%) compared with the placebo group (70.6%) and the severity of the AEs was mild to moderate, except for 2 subjects with severe events in the pregabalin group (one each of breast cancer and loss of consciousness). The most common all-causality AEs resulting in study discontinuation in the pregabalin group were somnolence, dizziness and insomnia. There were no serious or severe treatment-related AEs in either group. Pregabalin was well tolerated in this study and the AEs were consistent with the known safety profile of pregabalin.