PFIZER INC.

These results are supplied for informational purposes only.
Prescribing decisions should be made based on the approved package insert.
For publications based on this study, see associated bibliography.

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

THERAPEUTIC AREA AND FDA APPROVED INDICATIONS: See USPI.

NATIONAL CLINICAL TRIAL NO.: NCT00553475

PROTOCOL NO.: A0081163

PROTOCOL TITLE: Randomized, Double-Blind, Multicenter, Placebo-Controlled Study to Evaluate Efficacy and Safety of Pregabalin (CI-1008) in the Treatment for Pain Associated with Diabetic Peripheral Neuropathy

Study Center(s): 62 centers in Japan

Study Initiation and Completion Dates: 16 October 2007 to 21 March 2009

Phase of Development: Phase 3

Study Objective(s): To evaluate the efficacy and safety of pregabalin at 300 mg/day and 600 mg/day twice daily (BID) for pain associated with diabetic peripheral neuropathy.

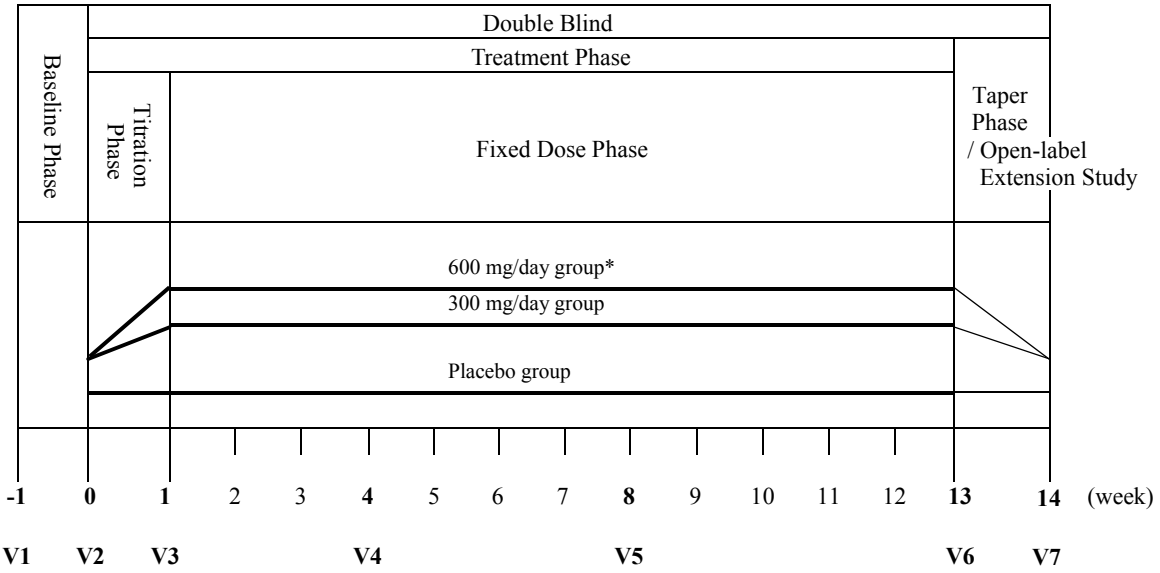
Primary objective:
- To evaluate the superiority of pregabalin at 300 mg/day over placebo in efficacy

Secondary objectives:
- To evaluate the superiority of pregabalin at 600 mg/day over placebo in efficacy
- To evaluate safety and tolerability of pregabalin

METHODS

Study Design: This was a randomized, double-blind, multicenter, placebo-controlled, parallel-group study in patients with pain associated with diabetic peripheral neuropathy. The study consisted of a 1-week baseline phase (baseline values were measured), a 13-week treatment phase (including a 1-week titration phase, and a 12-week fixed-dose phase), and a 1-week taper phase (only for subjects who did not enter the long-term study A0081164). Figure S1 shows an outline of the study design. Based on creatinine clearance (CLcr), subjects were classified into 2 strata and were each randomly assigned to 1 of 3 treatment groups (the placebo group, pregabalin 300 mg/day group, and 600 mg/day group) (Table S1).

Figure S1. Outline of the Study Design



*Patients randomized to the 600 mg/day treatment group received 300 mg/day for: 30 < creatinine clearance ≤ 60 mL/min. Creatinine clearance was estimated using the Cockcroft and Gault equations.

Table S1. Daily Dose Assigned Based on CLcr

Treatment group	Low CLcr	Normal CLcr
	30 < CLcr ≤60 mL/min	CLcr > 60 mL/min
Placebo	0 mg/day	0 mg/day
Pregabalin 300 mg/day	300 mg/day	300 mg/day
Pregabalin 600 mg/day	300 mg/day	600 mg/day

Number of Subjects (Planned and Analyzed):
Planned; 308 subjects (Placebo group: 132 subjects, Pregabalin 300 mg/day group: 132 subjects, Pregabalin 600 mg/day group: 44 subjects)
Analyzed; See Table S2

Table S2. Number of Subjects Analyzed

N (%)	Placebo	Pregabalin	
		300 mg/day	600 mg/day
Efficacy analysis population			
FAS	135 (99.3)	134 (98.5)	45 (100)
PPS	120 (88.2)	118 (86.8)	39 (86.7)
Safety analysis population			
Adverse events	135 (99.3)	134 (98.5)	45 (100)
Laboratory data	135 (99.3)	134 (98.5)	45 (100)

Diagnosis and Main Criteria for Inclusion: Male and female subjects aged 18 years or older who had been diagnosed with type 1 or 2 diabetes mellitus at least 1 year before, who were able to be diagnosed with painful, distal, symmetrical, sensorimotor polyneuropathy, due to diabetes at the start of the baseline phase (V1), and in whom the disease was considered to have developed at least 1 year before. Patients who had a score of 40 mm or

higher on the Visual Analogue Scale (VAS) of the Short-Form McGill Pain Questionnaire (SF-MPQ) at V1 and at the start of the double blind phase (V2) and who had evaluated and recorded their pain for at least 4 of the previous 7 days in a daily pain diary required to be kept until V2, with the mean score being 4 or higher. However, following patients were excluded: those who had been diagnosed with a malignant tumor within the past 2 years; those whose CLcr calculated according to the Cockcroft and Gault formula was 30 mL/min or lower; those who had pain that might affect the evaluation of "pain associated with diabetic peripheral neuropathy" or the self-rating; those who had skin conditions that might affect the evaluation of "pain associated with diabetic peripheral neuropathy" in the judgment of the investigator.

Study Treatment: Study drug was taken from the evening of V2. After a 1 week-titration phase, patients took pregabalin at a dose of 150 mg or 300 mg, or placebo, twice daily in the morning and evening, during a 12-week fixed-dose treatment phase until the visit day (V6) at Week 13 or discontinuation (final assessment point) [or until the visit day (V7) at Week 14 for patients who did not enter the long-term study].

Efficacy Evaluations:
Primary endpoint:
- The mean change from baseline in weekly mean pain score from daily pain diary scale at Week 13 (LOCF). [for which an 11-point numerical rating scale (0 to 10) is used]

Secondary endpoints:
- Weekly mean pain scores from the patient's daily pain diary [for which an 11-point numerical rating scale (0 to 10) is used]
- Responder rates (defined as 50% or more reduction in weekly mean pain score from baseline to endpoint)
- Short-Form McGill Pain Questionnaire (SF-MPQ)
- Weekly mean sleep interference scores from the patient's daily pain diary [for which an 11-point numerical rating scale(0 to 10) is used]
- Medical Outcomes Study (MOS)-Sleep Scale
- SF-36®
- The Patient Impression for subjective symptom
- The Patient Global Impression of Change (PGIC)
- The Clinical Global Impression of Change (CGIC)

Pharmacokinetic, Pharmacodynamic, and/or Other Evaluations: Plasma concentrations of pregabalin.

Safety Evaluations: Adverse events, weight, blood pressure, pulse rate, physical examinations, edema assessment, neurological examinations and ophthalmologic examinations, standard 12-lead electrocardiogram (ECG) and clinical laboratory test (hematology, serum chemistry, and urinalysis).

Statistical Methods:

Efficacy analysis

The analysis set for the primary and secondary efficacy analyses was defined as subjects who have received at least one dose of study drug and had both baseline and at least one post-baseline efficacy measurements.

The primary analysis compared pregabalin 300 mg/day group with the placebo group with respect to the change in the weekly mean pain score from baseline to the final assessment point. For the comparison, an analysis of covariance (ANCOVA) was used, with treatment and CLcr (estimated value) strata as factors, and the baseline weekly mean pain score as a covariate. A significance level for testing the treatment effect was 0.05. Moreover, to confirm the validity of the analysis results obtained at the final assessment point, the results were compared with those from the analysis based on the mixed-effects model.

As an important secondary analysis, the change in the weekly mean pain score from baseline to the final assessment point was compared between the 600 mg/day group and the placebo group. The same ANCOVA model as in the primary analysis was used. The following variables were also analyzed secondarily: The weekly mean pain scores from the daily pain diary for each week of the treatment phase, the responder rate (the proportion of subjects with ≥ 50% reduction in the weekly mean pain scores), SF-MPQ, MOS-Sleep Scale, SF-36®, the patient impression of subjective symptoms, PGIC and CGIC.

Safety analysis

The safety analysis set was defined as all subjects who had received at least one dose of the study drug. The safety analysis was conducted according to the Pfizer Data Standards, which define the standard procedures for reporting safety. Adverse events, laboratory data, vital signs, standard 12-lead ECG and neurological and ophthalmologic examinations were summarized by treatment group. All subjects who had discontinued the treatment were listed and their reasons for discontinuation were tabulated.

RESULTS

Subject Disposition and Demography: In the present study, 317 subjects were randomly assigned to one of the treatment groups. Of these, 314 subjects received study treatment, consisting of 135 subjects in the placebo group, 134 subjects in the 300 mg/day group and 45 subjects in the 600 mg/day group. Three of the randomized subjects discontinued the study without taking a dose of the study drug, due to the use of a restricted concomitant medication during the baseline phase, a low mean score based on the daily pain diary, and the use of a prohibited concomitant medication (Table S3).

Of those who received study treatment, 16 subjects in the placebo group, 20 subjects in the 300 mg/day group, and 13 subjects in the 600 mg/day group discontinued the study.

The most common reason for discontinuation was treatment-related adverse events, which occurred in 6 subjects in the placebo group, 10 subjects in the 300 mg/day group, and 12

subjects in the 600 mg/day group. In the placebo group, 7 subjects discontinued the study due to lack of efficacy.

Table S3. Subject Disposition [Number (%) of subjects]

	Placebo	Pregabalin	
		300 mg/day	600 mg/day
Assigned to Study Treatment	136	136	45
Treated	135	134	45
Completed	119 (87.5)	114 (83.8)	32 (71.1)
Discontinued	16 (11.8)	20 (14.7)	13 (28.9)
Related to Study Drug	13	11	12
Adverse event	6	10	12
Lack of efficacy	7	1	0
Not Related to Study Drug	3	9	1
Adverse event	1	7	1
Other	1	1	0
Subject no longer willing to participate in study	1	1	0

Regarding the gender composition of the safety analysis set, 237 subjects were males and 77 subjects were females. The age range was 35 to 85 years, and 119 subjects (37.9%) were aged 65 years or older. The estimated CLcr (estimated baseline CLcr), calculated from the serum creatinine data at V1, ranged from 31.0 to 258.0 mL/min, with the mean of 97.5 mL/min. Thirty-four subjects were classified into the low CLcr stratum, whereas 280 subjects were classified into the normal CLcr stratum.

Efficacy Results: Regarding the change in the weekly mean pain score at the final assessment point in the FAS as the primary analysis set, the 300 mg/day and 600 mg/day groups were statistically significantly superior to the placebo group (Table S4). In the PPS as well, the 300 mg/day and 600 mg/day groups were statistically significantly superior to the placebo group, supporting the robustness of the results obtained in the FAS.

Table S4. Mean Pain Score Change from Baseline to Endpoint (FAS)

	Number of Subject	Mean	Mean Change	Difference from Placebo[a]	
		Least Squares[a] (SE)	Least Squares[a] (SE)	Least Squares [95%CI]	p-Values
Placebo	135	4.83 (0.21)	−1.20 (0.21)	−	−
Pregabalin 300 mg/day	134	4.20 (0.22)	−1.82 (0.22)	−0.63 [−1.09, −0.17]	0.0075
Pregabalin 600 mg/day	45	4.08 (0.32)	−1.94 (0.32)	−0.74 [−1.39, −0.09]	0.0254

SE=Standard error; CI=Confidence interval.
[a]ANCOVA with the treatment groups and the CLcr strata as factors and baseline values as covariates

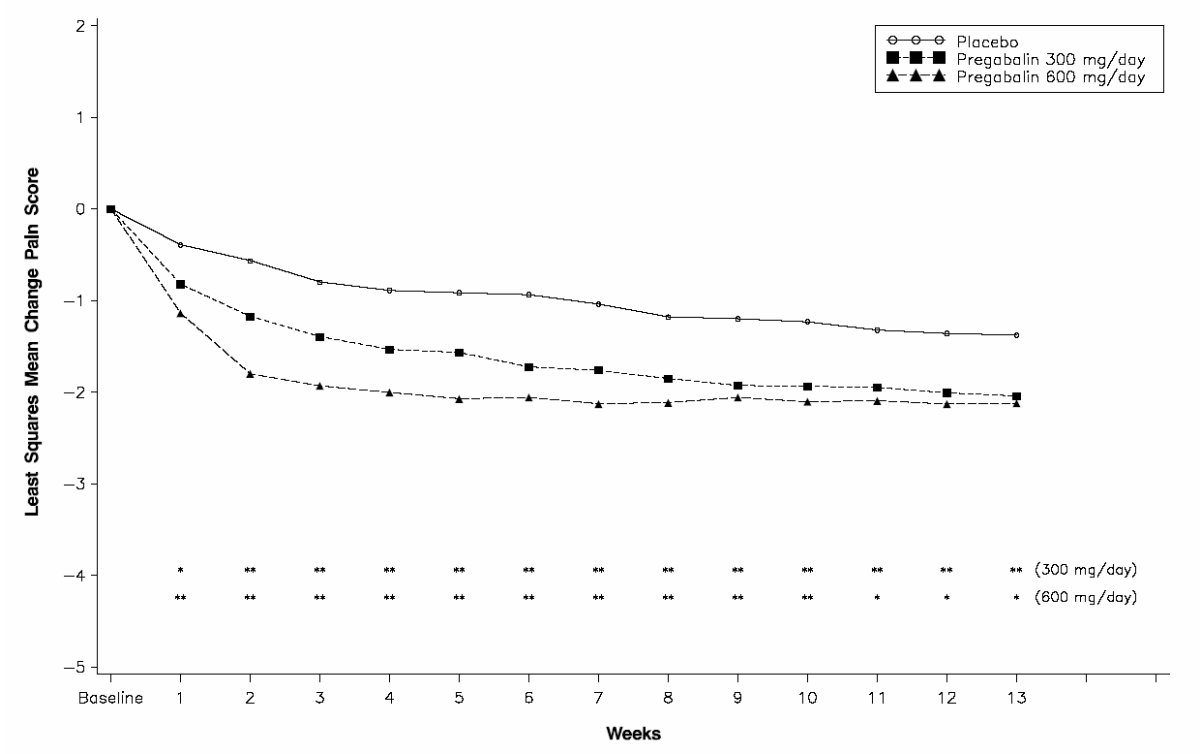
Regarding the weekly mean pain score in the FAS, both the 300 mg/day and 600 mg/day groups were statistically significantly superior to the placebo group from Week 1, and the significant differences were maintained up to Week 13 (Table S5, Figure S2). In the PPS as well, the 300 mg/day and 600 mg/day groups were statistically significantly superior to the placebo group, except for the score in the 300 mg/day group at Week 1.

Table S5. Weekly Mean Pain Scores Change from Baseline: Results of Mixed Model Repeated Measures Analysis (FAS)

	Number of Subject	Mean Score Least Squares (SE)	Mean Change Least Squares (SE)	Difference from Placebo Least Squares [95%CI]	p-Values
Week 1					
Placebo	135	5.64 (0.17)	-0.39 (0.17)	–	–
300 mg/day	134	5.21 (0.17)	-0.82 (0.17)	-0.43 [-0.82, -0.05]	0.0287
600 mg/day	45	4.89 (0.26)	-1.14 (0.26)	-0.75 [-1.29, -0.20]	0.0073
Week 2					
Placebo	133	5.46 (0.17)	-0.57 (0.17)	–	–
300 mg/day	132	4.86 (0.17)	-1.17 (0.17)	-0.61 [-1.00, -0.22]	0.0021
600 mg/day	41	4.23 (0.26)	-1.80 (0.26)	-1.23 [-1.78, -0.69]	<0.0001
Week 3					
Placebo	131	5.23 (0.17)	-0.80 (0.17)	–	–
300 mg/day	129	4.63 (0.17)	-1.40 (0.17)	-0.60 [-0.99, -0.21]	0.0026
600 mg/day	41	4.10 (0.26)	-1.93 (0.26)	-1.13 [-1.69, -0.58]	<0.0001
Week 4					
Placebo	130	5.14 (0.17)	-0.89 (0.17)	–	–
300 mg/day	128	4.50 (0.17)	-1.53 (0.17)	-0.64[-1.03, -0.25]	0.0012
600 mg/day	41	4.03 (0.26)	-2.00 (0.26)	-1.11 [-1.67, -0.56]	<0.0001
Week 5					
Placebo	130	5.11 (0.17)	-0.91 (0.17)	–	–
300 mg/day	125	4.46 (0.17)	-1.57 (0.17)	-0.65 [-1.04, -0.26]	0.0011
600 mg/day	38	3.96 (0.27)	-2.07 (0.27)	-1.16 [-1.72, -0.60]	<0.0001
Week 6					
Placebo	128	5.09 (0.17)	-0.94 (0.17)	–	–
300 mg/day	125	4.31 (0.17)	-1.72 (0.17)	-0.79 [-1.18, -0.40]	<0.0001
600 mg/day	37	3.97 (0.27)	-2.06 (0.27)	-1.12 [-1.68, -0.56]	<0.0001
Week 7					
Placebo	125	4.99 (0.17)	-1.04 (0.17)	–	–
300 mg/day	124	4.27 (0.17)	-1.76 (0.17)	-0.72 [-1.12, -0.33]	0.0003
600 mg/day	36	3.90 (0.27)	-2.13 (0.27)	-1.09 [-1.66, -0.52]	0.0002
Week 8					
Placebo	125	4.85 (0.17)	-1.18 (0.17)	–	–
300 mg/day	123	4.18 (0.17)	-1.85 (0.17)	-0.67 [-1.07, -0.28]	0.0008
600 mg/day	36	3.91 (0.27)	-2.12 (0.27)	-0.94 [-1.51, -0.36]	0.0014
Week 9					
Placebo	123	4.83 (0.17)	-1.20 (0.17)	–	–
300 mg/day	121	4.10 (0.17)	-1.93 (0.17)	-0.73 [-1.12, -0.33]	0.0003
600 mg/day	35	3.97 (0.28)	-2.06 (0.28)	-0.86 [-1.44, -0.28]	0.0036
Week 10					
Placebo	122	4.80 (0.17)	-1.23 (0.17)	–	–
300 mg/day	118	4.09 (0.18)	-1.93 (0.18)	-0.70 [-1.10, -0.31]	0.0005
600 mg/day	33	3.92 (0.28)	-2.10 (0.28)	-0.87 [-1.46, -0.29]	0.0034
Week 11					
Placebo	121	4.71 (0.17)	-1.32 (0.17)	–	–
300 mg/day	116	4.08 (0.18)	-1.95 (0.18)	-0.62 [-1.02, -0.22]	0.0023
600 mg/day	33	3.94 (0.28)	-2.09 (0.28)	-0.77 [-1.36, -0.18]	0.0105
Week 12					
Placebo	120	4.67 (0.17)	-1.36 (0.17)	–	–
300 mg/day	116	4.02 (0.18)	-2.01 (0.18)	-0.65 [-1.05, -0.25]	0.0016
600 mg/day	33	3.90 (0.29)	-2.13 (0.29)	-0.77 [-1.37, -0.18]	0.0111
Week 13					
Placebo	119	4.65 (0.17)	-1.38 (0.17)	–	–
300 mg/day	115	3.99 (0.18)	-2.04 (0.18)	-0.66 [-1.07, -0.26]	0.0013
600 mg/day	33	3.91 (0.29)	-2.12 (0.29)	-0.74 [-1.34, -0.14]	0.0152

SE = Standard error, CI = Confidence interval, 300 mg/day = Pregabalin 300 mg/day, 600 mg/day = Pregabalin 600 mg/day.

Figure S2. Weekly Mean Pain Scores Change from Baseline (FAS)



* p≤0.05 **p≤0.01 for comparison of each treatment group to placebo

An analysis in subjects classified by exposure to pregabalin, which was estimated by CLcr, showed that regarding the change in the weekly mean pain score at the final assessment point, the estimated 300 mg/day and 600 mg/day exposure groups were statistically significantly superior to the placebo group, both in the FAS (Table S6) and PPS.

Table S6. Mean Pain Scores Change from Baseline to Endpoint by Groups of Subjects with Expected Similar Plasma Concentrations (FAS)

	Number of Subject	Mean	Mean Change	Difference from Placebo [a]	
		Least Squares [a] (SE)	Least Squares [a] (SE)	Least Squares [95%CI]	p-Values
Placebo	135	4.76 (0.16)	-1.27 (0.16)	–	–
Expected Exposure 300 mg/day[b]	120	4.09 (0.17)	-1.93 (0.17)	-0.67 [-1.14, -0.19]	0.0058
Expected Exposure 600 mg/day[c]	59	4.12 (0.25)	-1.90 (0.25)	-0.64 [-1.23, -0.05]	0.0333

SE=Standard error; CI=Confidence interval.
[a]ANCOVA with the treatment groups by expected exposure as factors and baseline values as covariates
[b]Normal CLcr stratum in the Pregabalin 300 mg/day group.
[c]Includes the low CLcr stratum in the Pregabalin 300 mg/day group and the Pregabalin 600 mg/day group (the low CLcr stratum and normal CLcr stratum)

The responder rate was higher both in the 300 mg/day and 600 mg/day groups than in the placebo group, both in the FAS and PPS; in the PPS, a significant difference from the placebo group was noted for the 600 mg/day group.

Regarding the SF-MPQ at the final assessment point, the mean values of the sensory, affective, total, VAS and PPI scores in the 300 mg/day and 600 mg/day groups were

significantly superior to those observed in the placebo group, expect for the affective score in the 600 mg/day group.

Regarding the sleep interference score at the final assessment point, the 300 mg/day and 600 mg/day groups were statistically significantly superior to the placebo group.

Regarding the domains of the MOS-Sleep Scale, compared with the placebo group, the 300 mg/day group was statistically significantly superior in the domains of sleep interference, quantity of, and overall sleep problems index, and the 600 mg/day group was statistically significantly superior in the domain of sleep adequacy.

Regarding the patient impression of subjective symptoms, compared with the placebo group, the 300 mg/day group was statistically significantly superior in numbness and pain, and the 600 mg/day group was statistically significantly superior in paresthesia.

Compared with the placebo group, the 600 mg/day group was statistically significantly superior in PGIC, and the 300 mg/day and 600 mg/day groups were statistically significantly superior in CGIC.

Regarding the evaluation of SF-36® the 600 mg/day group was statistically superior to the placebo group in social functioning and vitality.

Regarding the presence or absence of allodynia or hyperalgesia at the final assessment point, no statistically significant differences from the placebo group were noted in either of the treatment groups.

Safety Results: The incidence of all-causality adverse events was the highest in the 600 mg/day group (93.3%, 42 subjects), followed by the 300 mg/day group (82.8%, 111 subjects) and the placebo group (73.3%, 99 subjects) (Table S7). The incidence of treatment-related adverse events was the highest in the 600 mg/day group (80.0%, 36 subjects), followed by the 300 mg/day group (56.7%, 76 subjects) and the placebo group (36.3%, 49 subjects).

Table S7. Summary of adverse events [Number (%) of subjects]

	All Causalities			Treatment Related		
	Placebo	Pregabalin		Placebo	Pregabalin	
		300 mg/day	600 mg/ day		300 mg/day	600 mg/ day
Subjects evaluable for adverse events	135	134	45	135	134	45
Subjects with adverse events (%)	99 (73.3)	111 (82.8)	42 (93.3)	49 (36.3)	76 (56.7)	36 (80.0)
Number of adverse events	232	299	123	76	161	79
Subjects with serious adverse events[a]	3	4	2	1	0	0
Subjects with severe adverse events (%)	1 (0.7)	2 (1.5)	3 (6.7)	0	1 (0.7)	1 (2.2)
Subjects discontinued due to adverse events (%)	7 (5.2)	17 (12.7)	13 (28.9)	6 (4.4)	10 (7.5)	12 (26.7)
Subjects with dose reduced or temporary discontinuation due to adverse events (%)	4 (3.0)	7 (5.2)	0	2 (1.5)	3 (2.2)	0

[a]The number of subjects with serious adverse events was based on the information from the safety database.

A summary of all-causality adverse events that occurred in > 5% of subjects in any pregabalin or placebo treatment group is shown in Table S8. The most commonly observed all-causality adverse events were somnolence, dizziness, oedema peripheral and weight increased in subjects treated with pregabalin, and were nasopharyngitis, somnolence, dizziness and oedema peripheral in subjects treated with placebo.

Table S8. Adverse Events Reported in >5% of subjects in Any Treatment Group [Number (%) of subjects]

MedDRA ver.11.1		Pregabalin	
Preferred Term	Placebo (N=135)	300 mg/day (N=134)	600 mg/day (N=45)
	n (%)	n (%)	n (%)
Constipation	1 (0.7)	4 (3.0)	3 (6.7)
Diarrhoea	5 (3.7)	3 (2.2)	3 (6.7)
Oedema	1 (0.7)	4 (3.0)	3 (6.7)
Oedema peripheral	8 (5.9)	19 (14.2)	8 (17.8)
Nasopharyngitis	20 (14.8)	16 (11.9)	4 (8.9)
Weight increased	5 (3.7)	17 (12.7)	7 (15.6)
Hypoglycaemia	3 (2.2)	3 (2.2)	3 (6.7)
Dizziness	9 (6.7)	26 (19.4)	18 (40.0)
Somnolence	12 (8.9)	28 (20.9)	18 (40.0)

The most commonly observed treatment-related adverse events were somnolence, dizziness, oedema peripheral and weight increased in subjects treated with pregabalin, being the same as all-causality adverse events, and were somnolence, dizziness and oedema peripheral in subjects treated with placebo. Severe all-causality adverse events were observed in 6 subjects (1 subject [pelvic fracture] in the placebo group, 2 subjects [diabetic nephropathy, pyrexia] in the 300 mg/day group, and 3 subjects [thermal burn, dehydration and hypoglycaemia, somnolence] in the 600 mg/day group). Severe treatment-related adverse events were observed in 2 subjects (1 subject [diabetic nephropathy] in the 300 mg/day and 1 subject [somnolence] in the 600 mg/day groups), but were confirmed to have resolved after discontinuation of the study drug. The severity of other adverse events was mild or moderate. The median time to the onset of somnolence or dizziness in either of the pregabalin groups was similar to that observed in the placebo group. The median duration of somnolence was 70.5 days in the 300 mg/day and 84.0 days in the 600 mg/day groups, that were longer than 53.0 days in the placebo group. The median duration of dizziness was longer (50.0 days) in the 300 mg/day group and shorter (30.0 days) in the 600 mg/day group than (47.5 days) in the placebo group.

The proportion of discontinued subjects due to adverse events was the highest in the 600 mg/day group (28.9%, 13 subjects), followed by the 300 mg/day group (12.7%, 17 subjects) and the placebo group (5.2%, 7 subjects). Of the adverse events considered to be most responsible for the discontinuation, dizziness (3 subjects in the 300 mg/day group, and 5 subjects in the 600 mg/day group) and somnolence (2 subjects in the 600 mg/day group) were observed in two or more subjects in the pregabalin groups (Table S9). All these events were confirmed to have been recovering or resolved.

Table S9. Summary of Withdrawals Due to Adverse Events Occurring in at Least 2 Subjects in Any Treatment Group [Number (%) of subjects]

MedDRA ver.11.1		Pregabalin	
Preferred Term	Placebo (N=135)	300 mg/day (N=134)	600 mg/day (N=45)
	n (%)	n (%)	n (%)
Dizziness	2 (1.5)	3 (2.2)	5 (11.1)
Somnolence	0	0	2 (4.4)

Serious adverse events were observed in 9 subjects (3 subjects in the placebo group, 4 subjects in the 300 mg/day group, and 2 subjects in the 600 mg/day group) (Table S10). All the serious adverse events observed in the pregabalin groups (6 subjects) were judged to have no causal relationship with the study drug. Regarding the outcomes of these 9 subjects, it was confirmed that hypertensive encephalopathy and brain stem infarction in one subject (in the 300 mg/day group) had been recovering, and that the other cases had resolved.

Table S10. Serious Adverse Events

MedDRA ver.11.1		Pregabalin	
Preferred Term	Placebo (N=135)	300 mg/day (N=134)	600 mg/day (N=45)
	n	n	n
Number of subjects	3	4	2
Atrial fibrillation	1	0	0
Nausea	1	0	0
Feeling abnormal	1	0	0
Peripheral coldness	1	0	0
Pyrexia	0	1	0
Diabetic foot infection	0	1	0
Herpes zoster	1	0	0
Blood glucose fluctuation	0	1	0
Dehydration	0	0	1
Hypoglycaemia	0	0	1
Pelvic fracture	1	0	0
Brain stem infarction	0	1	0
Hypertensive encephalopathy	0	1	0
Hypoaesthesia	1	0	0
Postrenal failure	0	0	1

The number of serious adverse events was based on the information from the safety database.

Regarding CK as a laboratory parameter, both the 300 mg/day and 600 mg/day groups showed greater changes towards an increase than the placebo group. No severe or serious adverse events related to abnormal laboratory values were observed. The number of subjects with an increase in body weight from baseline to the final assessment point was greater in the 300 mg/day and 600 mg/day groups than in the placebo group. Regarding blood pressure and pulse rate, no clinically significant changes were observed in the placebo group or either of the pregabalin groups.

Conclusion(s): The present study was conducted to evaluate the efficacy and safety of pregabalin administered twice daily (300 mg/day and 600 mg/day groups), in comparison with placebo, in patients with pain associated with diabetic peripheral neuropathy.

Regarding the change in the weekly mean pain score at the final assessment point, which was the primary endpoint, the pregabalin groups (300 mg/day and 600 mg/day groups) were statistically significantly superior to the placebo group. Regarding the weekly pain score, both of the pregabalin groups were statistically significantly superior to the placebo group from Week 1, and the significant differences were maintained up to the final assessment point. The responder rate was higher both in the 300 mg/day and 600 mg/day groups than in the placebo group, both in the FAS and PPS; in the PPS, a significant difference from the placebo group was noted for the 600 mg/day group. An analysis in subjects classified by exposure to pregabalin, which was estimated by CLcr, showed that regarding the change in the weekly mean pain score at the final assessment point, the estimated 300 mg/day and 600 mg/day exposure groups were statistically significantly superior to the placebo group. These findings demonstrate that pregabalin at doses of 300 mg/day or higher are effective when used in a twice-daily dosing regimen.

The most commonly observed adverse events were somnolence, dizziness, oedema peripheral and weight increased in subjects treated with pregabalin. The incidence of adverse events was higher in either of the pregabalin groups than in the placebo group. However, most of the adverse events were mild or moderate in severity, and the severe treatment-related adverse events (diabetic nephropathy and somnolence) and the adverse events (dizziness and somnolence) resulting in treatment discontinuation in subjects treated with pregabalin were confirmed to have resolved. All the serious adverse events observed in subjects treated with pregabalin were judged to have no causal relationship with the study drug. Regarding outcome, it was confirmed that one of these cases (hypertensive encephalopathy and brain stem infarction in the 300 mg/day group) had been recovering, and that the other cases had resolved. Thus, pregabalin was well tolerated in the present study.