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

THERAPEUTIC AREA AND FDA APPROVED INDICATIONS: See USPI.

NATIONAL CLINICAL TRIAL NO.: NCT00553280

PROTOCOL NO.: A0081164

PROTOCOL TITLE: An Open-Label Extension Safety and Efficacy Study of Pregabalin (CI-1008) for Pain Associated with Diabetic Peripheral Neuropathy

Study Center(s): Thirty-six (36) centers in Japan

Study Initiation and Completion Dates: 13 February 2008 to 20 January 2010

Phase of Development: Phase 3

Study Objective(s): To evaluate the long-term safety and efficacy of pregabalin at doses up to 600 mg/day for pain associated with diabetic peripheral neuropathy in patients who completed the 13-week treatment phase in the preceding study (Study A0081163).

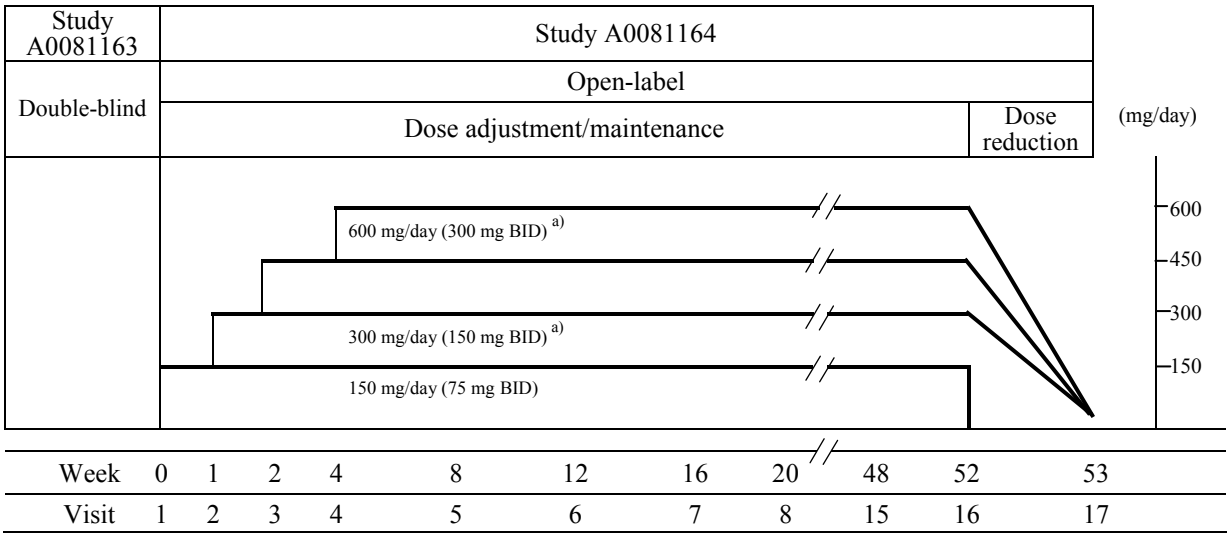
Primary Objective: To evaluate the long-term safety and tolerability of pregabalin

Secondary Objective: To evaluate the long-term efficacy of pregabalin

METHODS

Study Design: This study was a 53-week open-label long-term study in patients with pain associated with diabetic peripheral neuropathy. Subjects who were judged to meet the inclusion and exclusion criteria for this study were eligible for enrollment in this study following a visit at Week 13 (Visit 6) in the preceding study (Study A0081163). The study consisted of a 52-week dose adjustment/maintenance period and a 1-week dose reduction period (only for the subjects who received pregabalin at doses of 300 mg/day or higher), including a maximum of 17 study visits. The dose range of pregabalin was from 150 mg/day [75 mg twice daily (BID)] to 600 mg/day (300 mg BID). The maximum doses were 300 mg/day (150 mg BID in the morning and evening) for subjects with low creatinine clearance (CLcr) ($30 < CLcr \leq 60$ mL/min). The outline of the study design is shown in Figure S1.

Figure S1. Study Design



a) The maximum doses were 600 mg/day (300 mg BID) for subjects with normal creatinine clearance (CLcr) (CLcr > 60 mL/min) and 300 mg/day (150 mg BID) for subjects with low CLcr (30 < CLcr ≤ 60 mL/min). CLcr was estimated at Week 8 (Visit 5) in the preceding study (Study A0081163) using Cockcroft and Gault equation.

Number of Subjects (Planned and Analyzed): Planned, 120 subjects; Analyzed, 123 subjects

Diagnosis and Main Criteria for Inclusion: Patients with pain associated with diabetic peripheral neuropathy who had completed the 13-week treatment phase in the preceding study (Study A0081163), without any treatment-related serious adverse events or any compliance problems were eligible for the study.

Study Treatment: Subjects initiated to take the study drug at a dose of 75 mg in the evening of Day 1, and then 150 mg/day (75 mg BID) for 1 week from Day 2. Thereafter, subjects continued the treatment with pregabalin for 52 weeks, with the maximum doses of 300 mg/day (150 mg BID) for subjects with low CLcr (30 < CLcr ≤ 60 mL/min) and 600 mg/day (300 mg BID) for subjects with normal CLcr (CLcr > 60 mL/min). In consideration of safety and the effect on pain, the doses were adjusted by one step (150 mg/day) at each visit. Subjects treated with pregabalin at the doses of 300 mg/day or higher ended the treatment after a 1-week dose reduction period. However, for discontinued subjects for whom it was difficult to undergo the dose reduction period for safety reasons, or who would not take pregabalin for more than 1 week before the early termination visit, the treatment was discontinued without the dose reduction period. Subjects treated with pregabalin at a dose of 150 mg/day were to end the treatment without the dose reduction period. The investigator instructed subjects to take pregabalin for 52 or 53 weeks at the specified timing of administration (“before meal”, “after meal”) determined together with respective subjects in the preceding study (Study A0081163).

Efficacy Evaluations: Secondary endpoint: Short-Form McGill Pain Questionnaire (SF-MPQ)

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

Statistical Methods:

Sample size determination
A hundred twenty subjects was the targeted number of subjects necessary to investigate the safety and tolerability of the long-term use of pregabalin along with the overseas long-term study.

Efficacy analysis
The efficacy analysis set was defined as all subjects who had received at least one dose of the study drug and had been evaluated for efficacy after administration. The efficacy endpoints were SF-MPQ scores including sensory score, affective score, and total score, visual analog scale (VAS), and present pain intensity (PPI) score. The results were summarized descriptively, and no inferential testing was performed. The baseline for each efficacy endpoints was defined as either baseline of the preceding study (Study A0081163) for subjects randomized to pregabalin in Study A0081163 or that of this long-term study for subjects randomized to placebo in Study A0081163.

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 sponsor's standard procedures for collecting and reporting data on safety information. Safety data, such as adverse events, laboratory tests data, vital signs, standard 12-lead ECG, and neurological and ophthalmologic examinations, were summarized as descriptive statistics, and no inferential testing was performed.

RESULTS

Subject Disposition and Demography: A total of 123 subjects from the preceding study (Study A0081163) were enrolled in this study. Of these subjects, 97 subjects (78.9%) completed the study, and 26 subjects (21.1%) discontinued the study. The main reason for discontinuation was adverse events, which occurred in 19 subjects; related to the study drug in 12 subjects and unrelated to the study drug in 7 subjects. None of these subjects were excluded from the Full Analysis Set (FAS) for efficacy analysis or the safety analysis set (Table S1).

Regarding the gender composition of the 123 subjects, 100 subjects were males and 23 subjects were females. The age range was 36 to 85 years with the mean of 61.7 years, and 46 subjects (37.4%) were aged 65 years or older. The estimated CLcr calculated from the serum creatinine data at Week 8 (Visit 5) in the preceding study (Study A0081163), ranged from 36.0 to 251.0 mL/min, with the mean of 96.0 mL/min. Fourteen (14) subjects (11.4%) were classified into the low CLcr stratum, whereas 109 subjects (88.6%) were classified into the standard CLcr stratum.

The total exposure to pregabalin was 110 person-years.

Table S1. Subject Disposition and Subjects Analyzed

	Number of Subjects (%)	
Assigned to Study Treatment	123	
Treated	123	
Completed	97	(78.9)
Discontinued	26	(21.1)
Related to study drug	15	(12.2)
Adverse event	12	(9.8)
Lack of efficacy	3	(2.4)
Not related to study drug	11	(8.9)
Adverse event	7	(5.7)
Subject no longer willing to participate in study	3	(2.4)
Other [a)]	1	(0.8)
Analyzed for Efficacy		
Full Analysis Set (FAS)	123	(100)
Analyzed for Safety		
Adverse events	123	(100)
Laboratory data	123	(100)

a) One subject (Subject ID 10351012) was discontinued because it was judged that the long hospitalization influenced the evaluation of efficacy.

Efficacy Results: Efficacy results were summarized as descriptive statistics. All the mean SF-MPQ scores (sensory, affective and total scores) at endpoint (the time of last evaluation of each subjects during the adjustment/maintenance period; for subjects who discontinued the study, the time of early termination assessment) decreased from baseline, in conjunction with improvements in VAS and PPI score. The mean VAS and PPI score were 52.8 mm and 1.9 points, respectively, at baseline, then decreased to 27.4 mm and 1.2 points, respectively, at endpoint, with the mean changes of -25.4 mm and -0.7 points, respectively (Table S2). These results suggested an analgesic effect of long-term treatment with pregabalin.

Table S2. Summary of SF-MPQ

Time Point		Sensory Score	Affective Score	Total Score	VAS (mm)	PPI Score
Baseline [a)]	N	123	123	123	123	123
	Mean (SD)	7.4 (5.5)	2.0 (2.5)	9.4 (7.5)	52.8 (21.7)	1.9 (1.0)
	Median	6.0	1.0	8.0	57.0	2.0
	Range	0 to 30	0 to 12	0 to 42	1 to 98	0 to 5
Endpoint [b)]	N	123	123	123	123	123
	Mean (SD)	3.9 (4.8)	0.8 (1.9)	4.7 (6.5)	27.4 (22.7)	1.2 (0.9)
	Median	3.0	0.0	3.0	22.0	1.0
	Range	0 to 30	0 to 12	0 to 42	0 to 95	0 to 5
Change from baseline to endpoint [c)]	N	123	123	123	123	123
	Mean (SD)	-3.5 (5.1)	-1.2 (2.4)	-4.7 (6.8)	-25.4 (26.4)	-0.7 (1.1)
	Median	-3.0	0.0	-4.0	-22.0	-1.0
	Range	-23 to 12	-9 to 8	-32 to 20	-88 to 53	-4 to 3

VAS = visual analog scale, PPI = present pain intensity, SD = standard deviation
a) Baseline; either the preceding study (Study A0081163) baseline for subjects randomized to pregabalin in Study A0081163 or this open-label study baseline for subjects randomized to placebo in Study A0081163
b) Last evaluation of each subject during the adjustment/maintenance period or early termination assessment for subjects who discontinued the study
c) Negative values obtained as changes indicated an improvement in the pain symptom.

Safety Results: Of 123 subjects treated, 114 subjects (92.7%) experienced a total of 642 all-causality adverse events, which had worsened in severity compared with the level in the preceding study (Study A0081163) or which had newly occurred during this study, and 87 subjects (70.7%) experienced a total of 196 treatment-related adverse events (Table S3).

Table S3. Summary of Adverse Events

	All-causality	Treatment-related
Number of subjects analyzed for safety	123	123
Number of subjects with an AE (%)	114 (92.7)	87 (70.7)
Number of AEs	642	196
Number of subjects with an SAE [a)]	23	2
Number of subjects with a severe AE (%)	7 (5.7)	1 (0.8)
Number of subjects withdrawn due to AEs [b)] (%)	19 (15.4)	12 (9.8)
Number of subjects with dose reduction or temporary interruption due to AEs (%)	43 (35.0)	34 (27.6)

AE = adverse event, SAE = serious adverse event
a) Based on the information from the safety database on serious adverse events reported by 29 January 2010
b) Including 2 subjects who had withdrawn due to adverse events persisting from the preceding study (Study A0081163)

A summary of all-causality adverse events that occurred in ≥5% of subjects is shown in Table S4. The most common all-causality adverse events were nasopharyngitis (39 subjects, 31.7%), weight increased (35 subjects, 28.5%), somnolence (30 subjects, 24.4%), and dizziness (29 subjects, 23.6%).

Table S4. Summary of All-Causality Adverse Events Reported in ≥5% of Subjects

MedDRA (version 12.1) Preferred Term	Number of Subjects (%) (N=123)
Diabetic retinopathy	9 (7.3)
Visual acuity reduced	7 (5.7)
Constipation	11 (8.9)
Diarrhoea	8 (6.5)
Face oedema	10 (8.1)
Oedema	9 (7.3)
Oedema peripheral	21 (17.1)
Nasopharyngitis	39 (31.7)
Contusion	8 (6.5)
Fall	14 (11.4)
Weight increased	35 (28.5)
Hypoglycaemia	7 (5.7)
Arthralgia	7 (5.7)
Pain in extremity	7 (5.7)
Dizziness	29 (23.6)
Somnolence	30 (24.4)
Eczema	10 (8.1)

The most common treatment-related adverse events were somnolence (28 subjects, 22.8%), weight increased (27 subjects, 22.0%), and dizziness (25 subjects, 20.3%). Most of adverse events were mild or moderate in severity. Eight (8) severe all-causality adverse events were observed in 7 subjects (5.7%), but all except osteonecrosis were judged unrelated to study drug. Osteonecrosis was an adverse event for this 70-year-old subject who had pre-existing lumber spinal stenosis, and the investigator judged that the causality with the study drug could not be excluded as a possibility. Osteonecrosis was subsequently confirmed to have resolved following discontinuation of study treatment.

Nineteen (19) subjects (15.4%) discontinued study treatment due to adverse events (including 2 subjects who discontinued study treatment due to adverse events persisting from the preceding study). The events observed in 12 subjects (9.8%) were judged to be related to the study drug. The only adverse event leading to discontinuation reported in more than 1 subject was dizziness (2 subjects) (Table S5). Two (2) subjects experienced treatment-related serious adverse events leading to discontinuation (cerebral infarction and osteonecrosis in 1 subject each); however, each was resolving or resolved. The outcome assessment including the follow-up revealed that except liver disorder in 1 subject, other treatment-related adverse events leading to discontinuation had also been resolving or had resolved.

Table S5. Summary of All-Causality Adverse Events Resulted in Withdrawal from the Study [a)]

MedDRA (version 12.1) Preferred Term	Number of Subjects (%) (N=123)
Neutropenia	1 (0.8)
Atrioventricular block complete	1 (0.8)
Oedema	1 (0.8)
Oedema peripheral	1 (0.8)
Liver disorder	1 (0.8)
Femoral neck fracture	1 (0.8)
Fracture	1 (0.8)
Heat stroke	1 (0.8)
Neutrophil count decreased	1 (0.8)
Diabetes mellitus inadequate control [a)]	1 (0.8)
Back pain	1 (0.8)
Osteonecrosis	1 (0.8)
Spondylolisthesis	1 (0.8)
Cerebral infarction	1 (0.8)
Dizziness	2 (1.6)
Somnolence	1 (0.8)
Tremor	1 (0.8)
Anxiety disorder [a)]	1 (0.8)

a) Included 2 subjects who discontinued study treatment due to adverse events persisting from the preceding study

Forty-three (43) subjects (35.0%) reduced the dose of the study drug or temporarily discontinued the study drug due to adverse events, of which, the events observed in 34 subjects (27.6%) were considered as treatment-related. All of the adverse events leading to dose reduction or temporary discontinuation were mid or moderate in severity, and no severe adverse events were observed.

A total of 29 serious adverse events were reported in 23 subjects. No deaths were reported. Treatment-related serious adverse events were observed in 2 subjects (cerebral infarction and osteonecrosis in 1 subject each). Regarding the outcomes of the serious adverse events, hepatic neoplasm malignant and Meniere's disease in 1 subject each, which were both considered as unrelated to study drug, were reported as not resolved, but the events in other 21 subjects were confirmed to have been resolving or have resolved (Table S6).

Table S6. Serious Adverse Events

Sex	Age	MedDRA (ver.12.1) Preferred Term	Daily Dose [a] (mg/day)	Event Onset Day [b]	Investigator Causality [c]	Action Taken to Study Drug	Outcome
M	77	Lipoma	525	365	Other	No action taken	Recovered
M	52	Hyperglycaemia	300	44	Other	No action taken	Recovered
M	73	Femoral neck fracture	300	245	Other	Permanently discontinued	Recovered
F	68	Femur fracture	300	90	Other	No action taken	Recovered
	69	Hepatic neoplasm malignant	0	395	Other	No action taken [d]	Not recovered
M	44	Hand fracture	600	182	Other	Temporarily interrupted	Recovering
F	58	Spondylolisthesis	225	357	Other	Permanently discontinued	Recovering
M	68	Atrioventricular block complete	525	194	Other	Permanently discontinued	Recovering
F	70	Hypoglycaemia	150	314	Other	No action taken	Recovered
M	59	Pneumonia	300	239	Other	No action taken	Recovered
		Renal impairment	300	255	Other	No action taken	Recovered
M	76	Pneumonia	300	75	Other	No action taken	Recovered
M	57	Pneumonia	600	273	Other	No action taken	Recovered
F	46	Thermal burn	450	36	Other	No action taken	Recovering
M	83	Myocardial ischaemia	0	202	Other	No action taken [d]	Recovering
		Arteriosclerosis obliterans	0	202	Other	No action taken [d]	Recovered
M	48	Diabetic gangrene	300	14	Other	No action taken	Recovering
		Cellulitis	600	247	Other	No action taken	Recovering
M	59	Spinal osteoarthritis	600	63	Other	No action taken	Recovered
	60	Lumbar spinal stenosis	600	138	Other	No action taken	Recovered
M	57	Cellulitis	600	50	Other	No action taken	Recovered
		Diabetes mellitus inadequate control	525	29	Other	No action taken	Recovered
M	67	Back pain	600	169	Other	Permanently discontinued	Recovered
F	70	Cerebral infarction	150	225	Study drug	Permanently discontinued	Recovering
M	69	Meniere's disease	300	197	Other	No action taken	Not recovered
M	63	Cerebral infarction	300	308	Other	No action taken	Recovered [e]
M	70	Osteonecrosis	600	262	Study drug	Permanently discontinued	Recovered
F	61	Depression	0	385	Other	No action taken [d]	Recovering
F	78	Transient ischaemic attack	300	232	Other	No action taken	Recovered

M = male, F= female

a) Dose at onset of the serious adverse event

b) Days were relative to the day of starting treatment with pregabalin in this study (Day 1).

c) Causality was defined as the relationship between the study drug and the serious adverse event.

d) No action taken due to post-treatment event

e) The subject was assessed to have recovered with sequelae because of persisting numbness and strange feeling on the left side of the body without disabling condition.

The most commonly observed laboratory test abnormalities (with an incidence of 20% or higher, regardless of whether the baseline level was within the reference range or not) were

blood glucose, HbA_{1c}, and triglyceride exceeding the reference ranges as well as sugar urinary present, urinary protein positive and urinary occult blood positive.

Regarding body weight, clinically significant weight increased (increase of 7% or more from baseline at last examination) was observed in 21 subjects (17.1%). On physical examination, clinically significant changes compared to baseline of the preceding study were found in 13 subjects (10.6%).

Regarding oedema, no severe or serious adverse events were observed. Two (2) subjects discontinued study treatment due to oedema (oedema and oedema peripheral in 1 subject each), and both events were judged to be related to study drug. However, the outcome assessment including the follow-up confirmed that both events had resolved.

Neurological examination revealed muscle weakness (dorsiflexion of ankle) in 3 subjects for right and 2 subjects for left, and achilles tendon reflex decreased in 10 subjects for right and 11 subjects for left. The results of pin prick and vibration test showed worsening in 16 to 29 subjects at individual evaluated site. Regarding coordination (gait), 3 subjects experienced worsening of gait function.

On ophthalmologic examination, of those subjects without baseline abnormality on visual field testing (confrontation test), 2 subjects (1 subject each for left and right) were found to have new abnormal findings at the last observation. Funduscopy revealed clinically significant changes in 18 subjects.

On ECG, the cardiac adverse events (adverse events in MedDRA system organ class of cardiac disorders) were reported in 6 subjects of 19 subjects with clinically significant abnormalities observed at the completion or discontinuation of this study.

CONCLUSION(S): The present study was conducted to evaluate the long-term safety and efficacy of pregabalin administered BID at doses up to 600 mg/day for pain associated with diabetic peripheral neuropathy in patients who had completed the 13-week treatment phase in the preceding phase 3 study (Study A0081163).

The total exposure to pregabalin was 110 person-years.

The SF-MPQ scores as well as VAS and PPI score at endpoint showed improvements from baseline, suggesting the pain relief effect of long-term treatment with pregabalin.

The most common treatment-related adverse events were somnolence, weight increased, and dizziness. Most of the adverse events were mild or moderate in severity. Severe adverse events were observed in 7 subjects. Of those subjects with severe adverse events, 1 subject had a severe treatment-related adverse event, which was confirmed to have resolved. Serious adverse events were reported in 23 subjects. Serious adverse events observed in 2 subjects (cerebral infarction and osteonecrosis, in 1 subject each) were considered as treatment-related; however each was assessed as resolving or resolved. Overall, in outcome assessment of serious adverse events, 2 subjects (hepatic neoplasm malignant and Meniere's disease in 1 subject each; both considered as unrelated) were reported as not recovered, whereas other 21 subjects were confirmed to have been recovering or have recovered. No death was reported

in this study. The results showed that the adverse event profile observed was similar to that of the preceding study (Study A0081163), without new safety concerns over the long-term use of pregabalin. Thus, pregabalin was safe and well tolerated in this long-term study.