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

THERAPEUTIC AREA AND FDA APPROVED INDICATIONS: See USPI.

NATIONAL CLINICAL TRIAL NO.: NCT00424372

PROTOCOL NO.: A0081121

PROTOCOL TITLE: A Long-Term Study to Evaluate Safety and Efficacy of Pregabalin in the Treatment of Postherpetic Neuralgia

Study Centers: Thirty-four (34) centers in Japan

Study Initiation and Completion Dates: 12 January 2007 to 19 August 2008

Phase of Development: Phase 3

Study Objectives: To assess the safety and efficacy of the long-term use of pregabalin at doses of 150 to 600 mg/day twice daily (BID) in patients with postherpetic neuralgia who have completed a 13-week dosing in Study A0081120

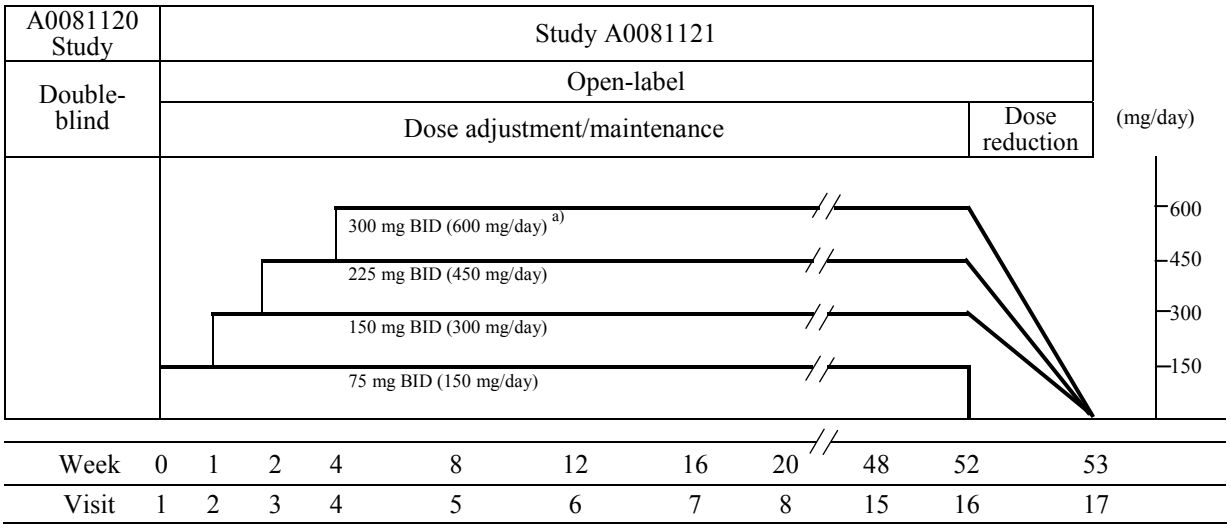
Primary Objective: To evaluate the safety of the long-term use of pregabalin

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

METHODS

Study Design: This study was a 53-week open-label long-term study in patients with postherpetic neuralgia. Patients completing Study A0081120 were eligible for enrollment in this study. The study consisted of a 52-week dose adjustment/maintenance period and a 1-week dose reduction period, including 17 study visits. Details are shown in Figure S1.

Figure S1. Study Design



a) Maximum doses were 150 mg BID [300 mg/day; 30 < creatinine clearance (CLcr) ≤ 60 mL/min] and 300 mg BID (600 mg/day; CLcr > 60 mL/min). CLcr was estimated at Visit 1 using Cockcroft and Gault equation.

Number of Subjects (Planned and Analyzed): Planned, 120; analyzed, 126.

Diagnosis and Main Criteria for Inclusion: Patients with postherpetic neuralgia who completed the 13-week treatment regimen in the preceding double-blind Study A0081120 and had no serious adverse events or issues with compliance were eligible for the study.

Study Treatment: Subjects initiated study drug at 75 mg in the evening of Day 1, and then 75 mg BID (150 mg/day) for 1 week from Day 2. Subsequent dose modifications were based on subjects' safety and efficacy response and the maximum doses were 150 mg BID (300 mg/day) for subjects with low creatinine clearance (CLcr) (30 < CLcr ≤ 60 mL/min) and 300 mg BID (600 mg/day) for subjects with normal CLcr (CLcr > 60 mL/min). Subjects receiving 150 mg BID (300 mg/day) or more were tapered off medication over a 1-week period when they stop the study drug. Subjects receiving 75 mg BID (150 mg/day) could stop the study drug without a dose reduction period. During the study, subjects were instructed to take study medication before or after a meal as was done in Study A0081120.

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

Pharmacokinetic Evaluations: Secondary endpoint: Plasma concentration of pregabalin.

Safety Evaluations: Primary endpoints: Adverse events, body weight, blood pressure, pulse rate, physical examination, edema assessment, neurological/ophthalmologic assessments, 12-lead electrocardiogram and laboratory tests (hematology, serum chemistry and urinalysis).

Statistical Methods:

Sample Size Determination: A total of 120 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 (Study 1008-198).

Efficacy Analysis: The analysis set was defined as full analysis set (FAS) which included all subjects who had received at least one dose of study drug and who had post dosing efficacy assessment. Efficacy endpoints were evaluated using the scores of the SF-MPQ; total score, sensory score, affective score, visual analog scale (VAS), and present pain intensity (PPI). The results were summarized descriptively, and no inferential testing was performed.

Pharmacokinetic Analysis: Since pharmacokinetic assessment was added after the start of the study, the assessment was performed for subjects with newly submitted written consents to collect blood samples for the pharmacokinetic evaluation. To evaluate pharmacokinetics in subjects with normal and with decreased renal function, comparison was made between the measured plasma concentration and the concentration predicted by pharmacokinetic models. The pharmacokinetic data will be merged with other pregabalin studies' data and analyzed using population pharmacokinetic model.

Safety Analysis: Subjects who had received at least one dose of study drug were included in the safety analysis set. Adverse events, laboratory tests results, vital signs (body weight, blood pressure, and pulse rate), 12-lead electrocardiogram and neurological examination/ophthalmologic assessments were summarized descriptively by treatment group. No inferential testing was performed on safety data.

RESULTS

Subject Disposition and Demography: A total of 126 subjects received the study drug. Of those, 31 subjects discontinued the study, with 18 subjects discontinuing due to adverse events (including laboratory abnormality) and 6 subjects due to lack of efficacy (Table S1).

The subjects included in the analysis consisted of 71 men and 55 women with an age range from 42 to 93 years. One-hundred-six (106) subjects (84.1%) were 65 years or older. The estimated baseline CLcr at Visit 1 ranged from 33.0 to 147.0 mL/min with a mean value of 70.2 mL/min, and 45 subjects (35.7%) had low CLcr ($30 < CLcr \leq 60$ mL/min) and 81 subjects (64.3%) had normal CLcr (CLcr > 60 mL/min). The disposition of subjects in the preceding phase 3 study (Study A0081120) was 33 subjects (26.2%) in the placebo group, 28 subjects (22.2%) in the pregabalin 150 mg/day group, 39 subjects (31.0%) in the 300 mg/day group, and 26 subjects (20.6%) in the 600 mg/day group.

The total exposure to pregabalin was calculated to be 107 person-years. Nearly half of the total pregabalin exposure was at a dose of ≥300 mg/day to <450 mg/day. The maximum dose administered in 90% or more of the subjects was ≥300 mg/day, and 29.4% of the subjects received 600 mg/day.

Table S1. Subject Disposition and Subjects Analyzed

	Number of Subjects	(%)
Assigned to Study Treatment	126	
Treated	126	
Completed	95	(75.4)
Discontinued	31	(24.6)
Subject Died	1	(0.8)
Related to Study Drug	21	(16.7)
Adverse event [a)]	11	(8.7)
Laboratory abnormality	4	(3.2)
Lack of efficacy	6	(4.8)
Not Related to Study Drug	9	(7.1)
Adverse event	3	(2.4)
Others [b)]	5	(4.0)
Subject no longer willing to participate in study	1	(0.8)
Analyzed for Efficacy	126	(100)
Analyzed for Safety		
Adverse events	126	(100)
Laboratory data	126	(100)

a) Including 1 adverse event which occurred during the preceding study (Study A0081120).
b) Impossible to visit study site (2 subjects), difficulty in visiting study site, deteriorating health, and protocol deviation (1 subject, each).

Efficacy Results: Mean SF-MPQ scores (sensory score, affective score, and total score) decreased from baseline to the last assessment. Improvements in both VAS and PPI were also observed, which suggest the sustained analgesic effect of pregabalin. The mean VAS and PPI scores were 62.0 mm and 2.8 points at baseline, and decreased to 28.3 mm and 1.4 points at Week 52, respectively (94 subjects assessed). Mean changes from baseline in these scores were −28.3 mm and −1.1 points, respectively (Table S2).

Table S2. Summary of SF-MPQ Scores, VAS and PPI Scores

Time Point		Sensory Score	Affective Score	Total Score	VAS (mm)	PPI
Baseline [a)]	N	126	126	126	126	126
	Mean (SD)	11.3 (7.0)	3.4 (3.1)	14.7 (9.7)	62.0 (19.0)	2.8 (1.0)
	Median	10.0	3.0	12.5	62.0	3.0
	Range	0 to 32	0 to 12	0 to 44	1 to 100	0 to 5
Week 52	N	94	94	94	94	94
	Mean (SD)	5.1 (5.6)	1.0 (1.8)	6.1 (7.2)	28.3 (22.9)	1.4 (0.9)
	Median	3.0	0.0	3.0	24.5	1.0
	Range	0 to 29	0 to 10	0 to 39	1 to 86	0 to 4
Endpoint	N	126	126	126	126	126
	Mean (SD)	6.7 (7.1)	1.7 (2.7)	8.2 (9.6)	33.7 (25.6)	1.7 (1.1)
	Median	4.0	0.0	4.0	32.5	1.0
	Range	0 to 33	0 to 11	0 to 42	1 to 100	0 to 5
Change From Baseline to Endpoint	N	126	126	126	126	126
	Mean (SD)	-4.8 (5.9)	-1.8 (2.8)	-6.5 (8.4)	-28.3 (23.8)	-1.1 (1.1)
	Median	-4.0	-1.0	-4.0	-28.0	-1.0
	Range	-24 to 14	-12 to 6	-34 to 18	-86 to 18	-4 to 2

VAS = visual analog scale, PPI = present pain intensity.
a) Baseline prior to initiation of active study drug (pregabalin); either the preceding study (Study A0081120) or this open-label study baseline.

Pharmacokinetic Results: The results will be summarized in a separate report for pregabalin population pharmacokinetics.

Safety Results: Of 126 subjects treated, 124 subjects (98.4%) experienced a total of 594 all-causality adverse events, which included events that worsened in severity when compared with the level of severity in the preceding study; 99 subjects (78.6%) experienced a total of 261 treatment-related adverse events (Table S3).

Table S3. Summary of Adverse Events

	All-causality	Treatment-related
Number of subjects analyzed for safety	126	126
Number of subjects with an AE (%)	124 (98.4)	99 (78.6)
Number of AEs	594	261
Number of subjects with an SAE (%)	15 (11.9)	4 (3.2)
Number of subjects with a severe AE (%)	5 (4.0)	2 (1.6)
Number of subjects withdrawn due to AEs (%)	17 (13.5)	13 (10.3)
Number of subjects with dose reduction or treatment suspension due to AEs (%)	34 (27.0)	28 (22.2)

AE = adverse event, SAE = serious adverse event.

A summary of all-causality adverse events that occurred in ≥5% of subjects analyzed for safety is presented in Table S4. The most common all-causality adverse events were dizziness (37 subjects, 29.4%), nasopharyngitis (34 subjects, 27.0%), peripheral edema (22 subjects, 17.5%), somnolence (22 subjects, 17.5%) and weight increased (19 subjects, 15.1%). The most common treatment-related adverse events were dizziness (36 subjects, 28.6%), peripheral edema (21 subjects, 16.7%), somnolence (19 subjects, 15.1%), and weight

increased (17 subjects, 13.5%). Most of these adverse events were mild or moderate in severity.

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

System Organ Class and preferred term (MedDRA version 11.0)	Number of subjects	(%)	(N = 126)
EYE DISORDERS	39	(31.0)	
Retinal hemorrhage	7	(5.6)	
Visual acuity reduced	7	(5.6)	
GASTROINTESTINAL DISORDERS	44	(34.9)	
Constipation	12	(9.5)	
Diarrhea	12	(9.5)	
Nausea	7	(5.6)	
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	40	(31.7)	
Peripheral edema	22	(17.5)	
INFECTIONS AND INFESTATIONS	49	(38.9)	
Nasopharyngitis	34	(27.0)	
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	21	(16.7)	
Fall	9	(7.1)	
INVESTIGATIONS	44	(34.9)	
Weight increased	19	(15.1)	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	37	(29.4)	
Arthralgia	7	(5.6)	
Osteoarthritis	7	(5.6)	
NERVOUS SYSTEM DISORDERS	58	(46.0)	
Dizziness	37	(29.4)	
Headache	8	(6.3)	
Somnolence	22	(17.5)	

A total of 17 subjects discontinued the study due to adverse events. A listing of all-causality adverse events that led to withdrawal is presented in Table S5.

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

MedDRA (version 11.0) preferred term	Number of subjects	(%)	(N=126)
Cardiac failure congestive	1	(0.8)	
Sick sinus syndrome	1	(0.8)	
Vision blurred	1	(0.8)	
Diarrhea	2	(1.6)	
Gastroduodenal ulcer	1	(0.8)	
Gingival pain	1	(0.8)	
Nausea	1	(0.8)	
Asthenia	1	(0.8)	
Chest pain	1	(0.8)	
Feeling abnormal	1	(0.8)	
Malaise	2	(1.6)	
Pain	1	(0.8)	
Pyrexia	1	(0.8)	
Gastroenteritis	1	(0.8)	
Joint dislocation	1	(0.8)	
Open fracture	1	(0.8)	
Radius fracture	1	(0.8)	
Spinal compression fracture	1	(0.8)	
Neutrophil count decreased	4	(3.2)	
Weight increased	1	(0.8)	
Lung neoplasm malignant	1	(0.8)	
Dizziness	2	(1.6)	
Dysarthria	1	(0.8)	
Hypoaesthesia	1	(0.8)	
Somnolence	3	(2.4)	
Urticaria	1	(0.8)	

Serious adverse events reported up to 20 October 2008 included 1 death due to completed suicide. In the investigator's opinion, this subject was primary caregiver to his ailing wife and exhausted, which was most likely the cause of the suicide and was not related to the study drug. Serious adverse events including this death were reported in 15 subjects. Serious adverse events in 4 subjects (5 events of chest pain, gastroduodenal ulcer, vertigo, dizziness, and headache) were assessed to be treatment-related by the investigator. In outcome assessment, 1 subject with gastroduodenal ulcer was assessed as recovering and other 3 subjects were confirmed as recovered (Table S6).

Table S6. Serious Adverse Events

Sex	Age	MedDRA (version 11.0) Preferred Term	Daily Dose [a] (mg/day)	Event Onset Day [b]	Investigator Causality [c]	Action Taken	Outcome
M	83	Cardiac failure congestive	300	90	Other	Permanently discontinued	Recovered
F	69	Chest pain	450	50	Study drug	Permanently discontinued	Recovered
M	85	Completed suicide	150	231	Other	No action taken	Death
M	79	Chronic obstructive pulmonary disease	600	85	Other	No action taken	Recovering
M	68	Lumbar spinal stenosis	300	218	Other	No action taken	Recovering
F	73	Spinal compression fracture	300	9	Other	No action taken	Recovered
		Pneumonia	300	86	Other	No action taken	Recovered
		Lung neoplasm malignant	300	108	Other	Permanently discontinued	Not Recovered
M	65	Atrial fibrillation	450	85	Other	No action taken	Not Recovered
M	81	Epistaxis	150	306	Other	No action taken	Recovered
		Emphysema	150	308	Other	No action taken	Recovered
F	75	Occult blood	150	62	Other	No action taken	Recovered
M	74	Gastroduodenal ulcer	450	248	Study drug	Permanently discontinued	Recovering
F	68	Asthma	600	92	Other	No action taken	Recovered
F	77	Malignant palate neoplasm	150	212	Other	Permanently discontinued	Unknown
M	76	Vertigo	300	288	Study drug	Temporarily interrupted	Recovered
F	69	Heat stroke	150	110	Other	No action taken	Recovered
		Radius fracture	150	107	Other	Permanently discontinued	Recovering
		Open fracture	150	107	Other	Permanently discontinued	Recovering
		Joint dislocation	150	107	Other	Permanently discontinued	Recovering
		Spinal compression fracture	150	107	Other	Permanently discontinued	Not Recovered
M	68	Dizziness	600	110	Study drug	Dose reduced	Recovered
		Headache	600	110	Study drug	Dose reduced	Recovered

M = Male, F = Female. a) Closest to onset of event. b) Days are relative to the day of starting active therapy (Day1). c) Causality defines the relationship to the study drug.

Laboratory abnormalities (occurring in ≥10% of subjects) included increases in triglycerides, low density lipoprotein (LDL) cholesterol, urinary occult blood, eosinophils, and creatine kinase (CK). Laboratory abnormalities leading to discontinuation of study treatment were reported in 4 subjects (decrease of neutrophils), and confirmed as recovered.

An increase in weight (≥7% increase from baseline) was observed in 22 subjects (17.5%), and reported as an adverse event in 19 subjects (15.1%); all increases were mild except in 3 cases, which were moderate in severity. There were no clinically significant changes in pulse rate or blood pressure. Clinically significant changes in physical examinations were noted in 29 subjects (23.0%).

Neurological examination revealed worsening of mild gait disturbance (3 subjects), mild muscle weakness (dorsiflexion of ankle; 1 subject each for left and right ankle), and decreased reflex of the achilles tendon (3 subjects each for left and right tendon).

Ophthalmologic examination revealed new abnormal findings on visual field testing (confrontation test) in 1 subject; however, there were no changes from baseline in all other subjects. Of 21 subjects who had clinically significant changes in funduscopy, 15 reported adverse events classified as eye disorders. These adverse events were all non-serious and mild in severity, and resolved in 9 of the 15 subjects.

Clinically significant findings on the electrocardiogram were observed in 30 subjects at the last assessment, and those in 6 subjects were reported as adverse events. In 1 of the 6 subjects, severe and serious congestive cardiac failure was noted, but this event was considered to be unrelated to the study drug. The remainder of the electrocardiographic events were non-serious and mild in severity.

CONCLUSIONS: This clinical study was conducted to assess the safety and efficacy of long-term, open-label pregabalin at doses of 150 to 600 mg/day BID in subjects with postherpetic neuralgia who completed 13-week of double-blind treatment in the preceding phase 3 study (Study A0081120).

Of 126 subjects enrolled in this open-label extension study, 95 subjects completed the study, and total exposure to pregabalin was calculated to be 107 person-years.

Changes from baseline in mean SF-MPQ scores, VAS, and PPI score, suggested that the pain-relieving effects were maintained with long-term use of pregabalin.

The most common adverse events were dizziness, peripheral edema, somnolence, and weight increase. Most of the adverse events were mild or moderate in severity.

Serious adverse events were reported in 15 subjects, including one death (suicide); of these, 5 events in 4 subjects, including chest pain, gastroduodenal ulcer, vertigo, dizziness, and headache, were treatment-related. The gastroduodenal ulcer in one subject was assessed as resolving, and those in other 3 subjects were confirmed as resolved.

Pregabalin was generally well tolerated with a similar adverse event profile as seen in Study A0081120. In addition, the results suggest that efficacy in postherpetic neuralgia is maintained with long-term treatment.