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

PROTOCOL NO.: A0081252

PROTOCOL TITLE: An Open-label Long-term Study of Pregabalin for the Treatment of Central Neuropathic Pain (Post Spinal Cord Injury Pain, Post Stroke Pain, and Multiple Sclerosis Pain)

Study Centers: Twenty seven (27) centers in Japan participated in the study and randomized subjects to study treatment.

Study Initiation and Final Completion Dates: 9 September 2010 to 15 March 2012

Phase of Development: Phase 3

Study Objectives:

Primary Objective: To assess the safety of the long-term use of pregabalin at doses up to 600 mg/day in subjects with central neuropathic pain (post spinal cord injury pain, post stroke pain, and multiple sclerosis pain).

Secondary Objective: To assess the efficacy of the long-term use of pregabalin at doses up to 600 mg/day.

METHODS

Study Design: This was an open-label, long-term, multicenter trial that was intended to confirm the safety, tolerability, and efficacy of pregabalin in a 53-week treatment (including a taper phase) in Japanese subjects with central neuropathic pain after spinal cord injury who had participated in the preceding study (A 17-Week, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multi-Center Trial of Pregabalin for the Treatment of Chronic Central Neuropathic Pain After Spinal Cord Injury [NCT00407745]), and those subjects with pain after cerebral stroke, or multiple sclerosis pain who newly joined the study. The maintenance doses of pregabalin were to be 150 mg/day, 300 mg/day, 450 mg/day, or 600 mg/day, divided twice daily (BID).

This trial was comprised of 3 phases:

- A 1- to 2-week screening phase (only for the subjects that were newly participating in the study);

- A 52-week treatment phase (a 4-week dose optimization phase and a 48-week fixed-dose treatment phase); and

- A 1-week taper phase (only for the subjects receiving daily doses of 300 mg, 450 mg, or 600 mg at the time of Visit 11).

The visit procedures are presented in Table 1 and Table 2.

Table 1. Schedule of Activities (Subjects That Were Shifted From the Preceding Study)

Protocol Activity		Preceding Study	Present Study										
			Treatment Phase										Taper Phase
	Evaluation Term	Week -2	Day 1[a]	Week 2	Week 4	Week 8	Week 12	Week 20	Week 28	Week 36	Week 44	Week 52/At Discontinuation (Before Dose Reduction)	Week 53/At Discontinuation (After Dose Reduction)
	Visit Point	V7	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12
	Allowable Days	—	—	±3	±3	±7	±7	±7	±7	±7	±7	±7	3
Informed consent			X										
Inclusion/exclusion			X										
Physical examination		(X)			X	X	X	X	X	X	X	X	X
Blood pressure/heart rate/body weight[b]		(X)			X	X	X	X	X	X	X	X	X
Edema/DVT assessment		(X)			X			X		X		X	X
Ophthalmologic examination			X					X				X[c]	
Neurological examination		(X)										X[c]	
12-lead ECG		(X)										X[c]	
Clinical labs: pregnancy test (serum)[d]		(X)			X		X	X		X		X[c]	
Clinical labs: hematology, chemistry		(X)			X		X	X		X		X[c]	
Clinical labs: urinalysis		(X)			X		X	X		X		X[c]	
SF-MPQ[e]			X	X	X	X	X	X	X	X	X	X	
mBPI-10[f]			X									X	
PHQ-8[g]			X										
S-STS[h]		(X)	(X)	X	X	X	X	X	X	X	X	X	X
Concomitant medications and therapies		(X)	(X)	X	X	X	X	X	X	X	X	X	X
Compliance		(X)		X	X	X	X	X	X	X	X	X	X
Telephone check[i]			←								→		
Adverse events		(X)	(X)	X	X	X	X	X	X	X	X	X	X

Table 1. Schedule of Activities (Subjects That Were Shifted From the Preceding Study)

(X) Conducted at V7 and/or V8 in the preceding study.
DVT = deep vein thrombosis; ECG = electrocardiogram; V = visit.

a. V1 in this study corresponded to V7 in the preceding study and V2 in this study corresponds to V8 in preceding study.
b. If the subject's disability did not allow the subject to be weighed safely it was permissible to indicate an estimated weight on the Case Report Form, and this was also noted in source documents.
c. Conducted at the after the treatment phase completion visit (V11 or V12).
d. Women only.
e. Short-Form McGill Pain Questionnaire (SF-MPQ).
f. Modified Brief Pain Inventory (10-item) (mBPI-10).
g. Patient Health Questionnaire-8 (PHQ-8).
h. Sheehan-Suicidality Tracking Scale (S-STS).
i. Subjects were called once during each period between V2 and V3, and between V3 and V4. Subjects were also called at least once during each visit interval between V4 and V11.

Table 2. Schedule of Activities (Subjects Newly Participating in This Study)

Protocol Activity			Present Study										
		Screening Phase	Treatment Phase										Taper Phase
	Evaluation Term	Week -2	Day 1	Week 2	Week 4	Week 8	Week 12	Week 20	Week 28	Week 36	Week 44	Week 52/At Discontinuation (Before Dose Reduction)	Week 53/At Discontinuation (After Dose Reduction)
	Visit Point	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12
	Allowable Days	7-14 Days Before V2	—	±3	±3	±7	±7	±7	±7	±7	±7	±7	3
Informed consent		X											
Inclusion/exclusion		X											
Physical examination		X			X	X	X	X	X	X	X	X	X
Blood pressure/heart rate/body weight[a]		X			X	X	X	X	X	X	X	X	X
Edema/DVT assessment		X			X			X		X		X	X
Ophthalmologic examination		X						X				X[b]	
Neurological examination		X										X[b]	
12 lead ECG		X										X[b]	
Clinical labs: pregnancy test (serum)[c]		X			X		X	X		X		X[b]	
Clinical labs: hematology, chemistry		X			X		X	X		X		X[b]	
Clinical labs: urinalysis		X			X		X	X		X		X[b]	
SF-MPQ[d]		X	X	X	X	X	X	X	X	X	X	X	
mBPI-10[e]			X									X	
PHQ-8[f]		X											
S-STS[g]		X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications and therapies		X	X	X	X	X	X	X	X	X	X	X	X
Compliance				X	X	X	X	X	X	X	X	X	X
Telephone check[h]			←							→			
Adverse events				X	X	X	X	X	X	X	X	X	X

Table 2. Schedule of Activities (Subjects Newly Participating in This Study)

DVT = deep vein thrombosis; ECG = electrocardiogram; V = visit.

a. If the subject's disability did not allow the subject to be weighed safely it was permissible to indicate an estimated weight on the Case Report Form, and this was also noted in source documents.
b. Conducted at the after the treatment phase completion visit (V11 or V12).
c. Women only.
d. Short-Form McGill Pain Questionnaire (SF-MPQ).
e. Modified Brief Pain Inventory (10-item) (mBPI-10).
f. Patient Health Questionnaire-8 (PHQ-8).
g. Sheehan-Suicidality Tracking Scale (S-STS).
h. Subjects were called once during each period between V2 and V3, and between V3 and V4. Subjects were also called at least once during each visit interval between V4 and V11.

Number of Subjects (Planned and Analyzed): The sample size of 100 subjects was planned to be evaluated in the study. About 103 subjects were actually randomized to study treatment. A breakdown of subjects with each disease was 30 or more for post spinal cord injury pain and 30 or more for post cerebral stroke pain.

Diagnosis and Main Criteria for Inclusion: In order to participate in this study, study subjects shifted from the preceding study that was conducted for the treatment of chronic central neuropathic pain after spinal cord injury. These subjects had to have completed assessments of all efficacy endpoints through to the end of the treatment phase of the preceding study (Visit 7).

Subjects that were newly enrolled in this study were male or female, at least 18 years of age, and had central neuropathic pain after cerebral stroke or central neuropathic pain associated with multiple sclerosis. A pain visual analog score (VAS) of 40 mm or more was required at both the start of the observation phase (Visit 1) and the start of the treatment phase (Visit 2).

Study Treatment: All subjects were given pregabalin BID, in the morning and evening. Subjects first received 75 mg of pregabalin in the evening of Day 1 and then 150 mg/day from Day 2 onwards during the first week. During the dose adjustment phase, the dosage (maintenance dose; 150 mg, 300 mg, 450 mg, or 600 mg/day) could have been adjusted by 1 step (±150 mg/day) in consideration of safety and efficacy based on the pain control observed at Visits 3 and 4, and at telephone contacts at Weeks 1 and 3. Dose escalation or reduction determined through a telephone contact was implemented on the day following the telephone contact.

In principle, subjects were to have remained at the same dosage during the maintenance phase. However, in consideration of efficacy and safety, 1 step (±150 mg/day) of dose adjustment was allowed at each visit from Visit 4 onward. Dose adjustments through telephone contact between study visits were not allowed during the maintenance phase. Under these conditions, subjects received pregabalin for a total of 52 weeks.

Subjects receiving at least 300 mg/day of pregabalin had a 1 week taper phase before completing the study treatment. However, in principle, the study was to be completed without the taper phase if the subject discontinued the study and was not able to comply with the taper phase because of safety or other reasons, or if the duration of dose interruption until the study discontinuation visit exceeded 1 week. Subjects receiving 150 mg/day of study drug also completed the study treatment without the taper phase.

Safety and Efficacy and Endpoints:

Safety Endpoint: Safety was considered the primary endpoint.

Efficacy Endpoints:

- Short-Form McGill Pain Questionnaire (SF-MPQ);
- Modified Brief Pain Inventory Interference Scale (10-Item) (mBPI-10).

Safety Evaluations: Safety endpoints included adverse events (AEs), physical examinations, blood pressure, heart rate, weight, edema assessment, deep vein thrombosis (DVT) assessment, ophthalmologic examinations, neurological examinations, 12-lead electrocardiogram (ECG), laboratory tests (hematology, chemistry, urinalysis, fasting lipid profile), Sheehan-Suicidality Tracking Scale (Sheehan-STS).

Statistical Methods:

All efficacy analyses were performed on the full analysis set defined as all subjects who received at least 1 dose of study medication and had both a baseline and at least 1 postbaseline VAS measurement.

All safety analyses were performed on the safety analysis set that consisted of all subjects who received at least 1 dose of study medication.

No inferential analyses was planned. Data obtained in this study were summarized descriptively (mean, standard deviation, median, quartiles, minimum and maximum for continuous variables, and frequency and percentage for categorical variables). The 95% confidence intervals for the mean based on the assumption that the data were normally distributed were also calculated. AEs were coded using the latest version of the Medical Dictionary for Regulatory Activities.

RESULTS

Subject Disposition and Demography: All of the 103 subjects were analyzed for efficacy and safety as presented in Table 3.

Table 3. Subject Disposition – Safety Analysis Set

Treated	**103**
Completed	84 (81.6)
Discontinued	19 (18.4)
Reason of discontinuations	
Not related to study drug	
Adverse event	3 (2.9)
Consent withdrawn	2 (1.9)
Related to study drug	
Adverse event	13 (12.6)
Insufficient clinical response	1 (1.0)
Analyzed for efficacy:	
Full analysis set	103 (100)
Analyzed for safety:	
Adverse events	103 (100)
Laboratory data	103 (100)
Safety analysis set	103 (100)

The demographic data are presented in the Table 4.

Table 4. Demographic Data – Safety Analysis Set

Number of Subjects	Male N=81	Female N=22	Total N=103
<18	0	0	0
18-44	13 (16.0)	2 (9.1)	15 (14.6)
45-64	46 (56.8)	14 (63.6)	60 (58.3)
≥65	22 (27.2)	6 (27.3)	28 (27.2)
Mean	57.4	59.4	57.9
SD	11.9	8.3	11.2
Range	29-80	39-74	29-80

N = number of subjects; SD = standard deviation.

Efficacy Results:

Short-Form McGill Pain Questionnaire (SF-MPQ): When evaluating the endpoints of the study, the mean total SF-MPQ, sensory pain, and affective pain scores decreased when compared with baseline scores, as presented in the Table 5.

Table 5. Summary of SF-MPQ Total, Sensory, and Affective Scores – FAS Population

Scores	Time Point	Scores		Score Change From Baseline[a]	
		N	Mean (SD)	N	Mean (SD)
Total scores	Baseline[b]	103	12.2 (9.1)		
	Visit 3 (Week 2)	103	8.0 (8.3)	103	-4.2 (6.0)
	Visit 4 (Week 4)	102	7.1 (7.7)	102	-5.2 (6.1)
	Visit 5 (Week 8)	99	6.9 (8.0)	99	-5.3 (6.5)
	Visit 6 (Week 12)	98	6.5 (8.3)	98	-5.7 (7.7)
	Visit 7 (Week 20)	95	5.9 (7.2)	95	-6.1 (7.0)
	Visit 8 (Week 28)	92	7.0 (8.5)	92	-5.1 (7.3)
	Visit 9 (Week 36)	91	7.1 (8.6)	91	-5.0 (7.4)
	Visit 10 (Week 44)	87	7.1 (8.6)	87	-4.4 (7.9)
	Visit 11 (Week 52)	85	6.7 (7.8)	85	-5.0 (7.4)
	Endpoint[c]	103	7.6 (8.8)	103	-4.6 (8.3)
Sensory scores	Baseline[b]	103	9.5 (7.1)		
	Visit 3 (Week 2)	103	6.4 (6.4)	103	-3.1 (4.7)
	Visit 4 (Week 4)	102	5.7 (5.9)	102	-3.9 (4.6)
	Visit 5 (Week 8)	99	5.5 (5.9)	99	-3.9 (4.9)
	Visit 6 (Week 12)	98	5.3 (6.2)	98	-4.2 (5.9)
	Visit 7 (Week 20)	95	4.8 (5.3)	95	-4.5 (5.4)
	Visit 8 (Week 28)	92	5.6 (6.5)	92	-3.8 (5.6)
	Visit 9 (Week 36)	91	5.6 (6.4)	91	-3.7 (5.3)
	Visit 10 (Week 44)	87	5.7 (6.5)	87	-3.1 (5.8)
	Visit 11 (Week 52)	85	5.3 (5.8)	85	-3.6 (5.6)
	Endpoint[c]	103	5.9 (6.3)	103	-3.6 (6.2)
Affective scores	Baseline[b]	103	2.7 (2.6)		
	Visit 3 (Week 2)	103	1.6 (2.3)	103	-1.1 (2.0)
	Visit 4 (Week 4)	102	1.4 (2.2)	102	-1.3 (2.2)
	Visit 5 (Week 8)	99	1.4 (2.4)	99	-1.3 (2.2)
	Visit 6 (Week 12)	98	1.2 (2.2)	98	-1.5 (2.4)
	Visit 7 (Week 20)	95	1.1 (2.2)	95	-1.6 (2.2)
	Visit 8 (Week 28)	92	1.4 (2.3)	92	-1.3 (2.2)
	Visit 9 (Week 36)	91	1.4 (2.5)	91	-1.3 (2.5)
	Visit 10 (Week 44)	87	1.4 (2.4)	87	-1.3 (2.6)
	Visit 11 (Week 52)	85	1.4 (2.3)	85	-1.4 (2.4)
	Endpoint[c]	103	1.7 (2.7)	103	-1.0 (2.7)

FAS = full analysis set; N = number of subjects; SF-MPQ = Short-Form McGill Pain Questionnaire, SD = standard deviation.

a. Negative change indicates an improvement of pain symptoms.
b. The last assessment on or before Day 1 in this study.
c. The last evaluation during the dose adjustment/maintenance step of the open-label, last observation carried forward.

Modified Brief Pain Inventory Interference Scale (10-Item) (mBPI-10): The total mBPI-10 score at the endpoint visit of the interim reporting suggested an improvement when compared with the baseline visit as presented in Table 6.

Table 6. Summary of Modified Brief Pain Inventory (10-Item) Total Scores – FAS Population

Scores	Scores		Score Change From Baseline[a]	
	N	Mean (SD)	N	Mean (SD)
Baseline[b]	103	3.9 (2.4)		
Endpoint[c]	101	2.5 (2.3)	101	-1.4 (2.4)

FAS = full analysis set; N = number of subjects; SD = standard deviation.
a. Negative change indicates an improvement of pain symptoms.
b. The last assessment on or before Day 1 in this portion of study.
c. The last evaluation during dose adjustment/maintenance step of open-label.

Safety Results: The treatment-emergent AEs are presented in Table 7, and treatment-emergent related AEs are presented in Table 8. The most frequently occurring treatment-emergent AEs were somnolence, weight increased, dizziness, nasopharyngitis, and edema peripheral. The most frequently occurring treatment-related, treatment-emergent AEs were somnolence, weight increased, dizziness, and edema peripheral.

Table 7. Treatment-Emergent Non-Serious Adverse Events by System Organ Class and Preferred Term for Events Having a Frequency Rate of >5 – All Causalities

	Pregabalin n (%)
Number (%) of subjects:	
Evaluable for adverse events	103
With adverse events	91 (88.3)
Number (%) of subjects with adverse events by:	
System organ class and MedDRA (v14.1) preferred term	
Eye disorders	7 (6.8)
Visual acuity reduced	7 (6.8)
Gastrointestinal disorders	8 (7.8)
Constipation	8 (7.8)
General disorders and administration site conditions	30 (29.1)
Feeling abnormal	7 (6.8)
Oedema peripheral	18 (17.5)
Thirst	7 (6.8)
Infections and infestations	26 (25.2)
Nasopharyngitis	26 (25.2)
Injury, poisoning and procedural complications	14 (13.6)
Contusion	8 (7.8)
Fall	13 (12.6)
Investigations	31 (30.1)
Weight increased	31 (30.1)
Musculoskeletal and connective tissue disorders	8 (7.8)
Back pain	8 (7.8)
Nervous system disorders	66 (64.1)
Dizziness	24 (23.3)
Hypoaesthesia	6 (5.8)
Somnolence	53 (51.5)
Skin and subcutaneous tissue disorders	14 (13.6)
Eczema	7 (6.8)
Rash	8 (7.8)

Subjects are only counted once per treatment for each row.
MedDRA (v14.1) coding dictionary applied.
MedDRA = Medical Dictionary for Regulatory Activities; n = number of subjects; v = version.

Table 8. Incidence of Treatment-Emergent Adverse Events (Treatment-Related)

Number of Subjects Evaluable for Adverse Events	Post Spinal Cord Injury Pain (N=38)		Post Stroke Pain (N=60)		Multiple Sclerosis Pain (N=5)	
System Organ Class and MedDRA (v14.1) Preferred Term	**n**	**%**	**n**	**%**	**n**	**%**
Blood and lymphatic system disorders	0	-	4	6.7	0	-
Anaemia	0	-	1	1.7	0	-
Leukopenia	0	-	1	1.7	0	-
Neutropenia	0	-	3	5	0	-
Cardiac disorders	0	-	1	1.7	0	-
Atrial fibrillation	0	-	1	1.7	0	-
Ear and labyrinth disorders	0	-	0	-	1	20
Vertigo	0	-	0	-	1	20
Eye disorders	4	10.5	3	5	1	20
Scleral haemorrhage	0	-	1	1.7	0	-
Vision blurred	1	2.6	1	1.7	1	20
Visual acuity reduced	3	7.9	2	3.3	0	-
Gastrointestinal disorders	5	13.2	8	13.3	0	-
Abdominal pain	1	2.6	0	-	0	-
Colonic polyp	1	2.6	0	-	0	-
Constipation	2	5.3	3	5	0	-
Diarrhoea	1	2.6	0	-	0	-
Dyspepsia	1	2.6	1	1.7	0	-
Epigastric discomfort	0	-	1	1.7	0	-
Nausea	0	-	3	5	0	-
Vomiting	0	-	1	1.7	0	-
General disorders and administration site conditions	10	26.3	22	36.7	1	20
Asthenia	1	2.6	2	3.3	0	-
Face oedema	0	-	1	1.7	0	-
Fatigue	1	2.6	2	3.3	0	-
Feeling abnormal	0	-	7	11.7	0	-
Generalised oedema	1	2.6	0	-	0	-
Malaise	1	2.6	0	-	0	-
Oedema	0	-	1	1.7	0	-
Oedema peripheral	7	18.4	11	18.3	0	-
Thirst	1	2.6	3	5	1	20
Hepatobiliary disorders	1	2.6	1	1.7	0	-
Hepatic function abnormal	0	-	1	1.7	0	-
Hepatic steatosis	1	2.6	0	-	0	-
Infections and infestations	1	2.6	0	-	0	-
Impetigo	1	2.6	0	-	0	-
Injury, poisoning and procedural complications	0	-	1	1.7	0	-
Fall	0	-	1	1.7	0	-
Investigations	11	28.9	29	48.3	1	20
Alanine aminotransferase increased	1	2.6	0	-	0	-
Aspartate aminotransferase increased	1	2.6	0	-	0	-
Blood alkaline phosphatase increased	0	-	1	1.7	0	-
Blood chloride decreased	1	2.6	0	-	0	-
Blood creatine phosphokinase increased	2	5.3	0	-	0	-
Blood lactate dehydrogenase increased	0	-	1	1.7	0	-
Blood potassium increased	1	2.6	0	-	0	-
Blood pressure increased	1	2.6	0	-	0	-
Blood sodium decreased	1	2.6	0	-	0	-
Creatinine renal clearance decreased	0	-	2	3.3	0	-
Differential white blood cell count abnormal	0	-	1	1.7	0	-
Haematocrit decreased	1	2.6	0	-	0	-

Table 8. Incidence of Treatment-Emergent Adverse Events (Treatment-Related)

Number of Subjects Evaluable for Adverse Events	Post Spinal Cord Injury Pain (N=38)		Post Stroke Pain (N=60)		Multiple Sclerosis Pain (N=5)	
System Organ Class and MedDRA (v14.1) Preferred Term	**n**	**%**	**n**	**%**	**n**	**%**
Haemoglobin decreased	1	2.6	0	-	0	-
Neutrophil count decreased	0	-	3	5	0	-
Weight increased	6	15.8	22	36.7	1	20
Metabolism and nutrition disorders	1	2.6	3	5	0	-
Decreased appetite	0		1	1.7	0	-
Hyperuricaemia	1	2.6	2	3.3	0	-
Musculoskeletal and connective tissue disorders	1	2.6	1	1.7	0	-
Muscle spasms	1	2.6	0	-	0	-
Muscular weakness	0	-	1	1.7	0	-
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	-	1	1.7	0	-
Oral neoplasm	0	-	1	1.7	0	-
Nervous system disorders	24	63.2	37	61.7	4	80
Ataxia	0	-	1	1.7	0	-
Burning sensation	0	-	1	1.7	0	-
Cerebral haemorrhage	0	-	1	1.7	0	-
Dizziness	6	15.8	16	26.7	1	20
Dizziness postural	0	-	1	1.7	0	-
Dysgeusia	0	-	1	1.7	0	-
Hemiparesis	0	-	1	1.7	0	-
Hyperreflexia	0	-	1	1.7	0	-
Hypoaesthesia	0	-	1	1.7	0	-
Loss of consciousness	0	-	1	1.7	0	-
Somnolence	21	55.3	25	41.7	4	80
Psychiatric disorders	0	-	1	1.7	0	-
Sleep disorder	0	-	1	1.7	0	-
Renal and urinary disorders	2	5.3	6	10	0	-
Haematuria	0	-	1	1.7	0	-
Neurogenic bladder	1	2.6	0	-	0	-
Pollakiuria	1	2.6	0	-	0	-
Renal impairment	0	-	3	5	0	-
Urinary incontinence	0	-	1	1.7	0	-
Urinary retention	0	-	1	1.7	0	-
Skin and subcutaneous tissue disorders	1	2.6	4	6.7	0	-
Alopecia	0	-	1	1.7	0	-
Eczema	0	-	2	3.3	0	-
Eczema nummular	0	-	1	1.7	0	-
Rash	1	2.6	1	1.7	0	-
Vascular disorders	1	2.6	2	3.3	0	-
Blood pressure fluctuation	0	-	1	1.7	0	-
Hypotension	1	2.6	1	1.7	0	-
Total preferred term events	73	-	147	-	9	-

MedDRA (v14.1) coding dictionary applied.
Adverse events and serious adverse events were not separated in the table.
MedDRA = Medical Dictionary for Regulatory Activities; n = number of subjects; v = version.

The treatment-emergent serious AEs are presented in the Table 9. One (1.0%) cerebral hemorrhage in a subject with post-stroke pain was determined to be treatment-related.

Table 9. Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term (All Causalities)

	n (%)
Number (%) of subjects:	
Evaluable for serious adverse events	103
With adverse events	19 (18.4)
Number (%) of subjects with adverse events by:	
System organ class and MedDRA (v14.1) preferred term	
Cardiac disorders	1 (1.0)
Arteriosclerosis coronary artery	1 (1.0)
Gastrointestinal disorders	5 (4.9)
Anal fistula	1 (1.0)
Colonic polyp	1 (1.0)
Inguinal hernia	1 (1.0)
Melaena	1 (1.0)
Tooth development disorder	1 (1.0)
Hepatobiliary disorders	1 (1.0)
Cholangitis acute	1 (1.0)
Infections and infestations	6 (5.8)
Cellulitis	2 (1.9)
Infected skin ulcer	1 (1.0)
Pneumonia	1 (1.0)
Sepsis	1 (1.0)
Urinary tract infection	1 (1.0)
Injury, poisoning and procedural complications	2 (1.9)
Femur fracture	1 (1.0)
Mucosal excoriation	1 (1.0)
Nervous system disorders	4 (3.9)
Cerebral haemorrhage	1 (1.0)
Cerebral infarction	2 (1.9)
Transient ischaemic attack	1 (1.0)
Psychiatric disorders	1 (1.0)
Psychotic disorder	1 (1.0)
Respiratory, thoracic and mediastinal disorders	1 (1.0)
Nasal polyps	1 (1.0)
Skin and subcutaneous tissue disorders	1 (1.0)
Ingrowing nail	1 (1.0)

Subjects were only counted once per treatment for each row.
MedDRA (v14.1) coding dictionary applied.
MedDRA = Medical Dictionary for Regulatory Activities; n = number of subjects; v = version.

Sixteen subjects (15.5%) discontinued the study treatment due to AEs. Of those, AEs reported in 13 subjects (12.6%) were determined treatment-related. Forty five subjects (43.7%) had dose reduction or interruption due to AEss, of which 41 (39.8%) were determined treatment-related.

No deaths were reported during this study.

The summary of significant changes in the physical examinations is presented in Table 10.

Table 10. Summary of Significant Changes in Physical Examination - All Subjects

	N=103
Number of subjects assessed*	103
Significant changes** since the Screening	32 (31.1)

* N is number of subjects with after the Screening.
** Any time during the study: All observations available after Day 1 of open-label.

Clinically significant systolic blood pressure increased (sitting) and diastolic blood pressure increased (sitting) occurred in 1 subject (1.0%) each at the endpoint. There was no change in pulse rates that was clinically significant.

Clinically significant weight increased (increase of 7% or higher from Baseline to final assessment) occurred in 14 subjects (13.6%).

The number of subjects with peripheral edema is presented in the Table 11.

Table 11. Edema Assessments: Peripheral Edema - All Subjects

	N=103	
	n	**%**
Baseline, N	103	
Absent	87	84.5
Trace	5	4.9
Pitting +1: edema of lower leg	9	8.7
Pitting +2: edema of lower leg to knee	2	1.9
Pitting +3: edema above knee and/or presacral edema	0	0
Week 4, N	101	
Absent	80	79.2
Trace	8	7.9
Pitting +1: edema of lower leg	8	7.9
Pitting +2: edema of lower leg to knee	4	4
Pitting +3: edema above knee and/or presacral edema	1	1
Week 20, N	93	
Absent	75	80.6
Trace	8	8.6
Pitting +1: edema of lower leg	3	3.2
Pitting +2: edema of lower leg to knee	7	7.5
Pitting +3: edema above knee and/or presacral edema	0	0
Week 36, N	90	
Absent	66	73.3
Trace	14	15.6
Pitting +1: edema of lower leg	7	7.8
Pitting +2: edema of lower leg to knee	3	3.3
Pitting +3: edema above knee and/or presacral edema	0	0
Week 52/early termination, N	100	
Absent	81	81
Trace	10	10
Pitting +1: edema of lower leg	7	7
Pitting +2: edema of lower leg to knee	2	2
Pitting +3: edema above knee and/or presacral edema	0	0
Week 53/early termination, N	78	
Absent	64	82.1
Trace	9	11.5
Pitting +1: edema of lower leg	5	6.4
Pitting +2: edema of lower leg to knee	0	0
Pitting +3: edema above knee and/or presacral edema	0	0

Baseline: The last assessment on or before Day 1 in this study.
N = total number of subjects; n = number of subjects in each subgroup.

The number of subjects with facial/periorbital and generalized or abdominal edema is presented in Table 12.

Table 12. Edema Assessments: Facial/Periorbital Edema, Generalized or Abdominal Edema - All Subjects

	N=103
Facial/Periorbital	
Baseline, n	103
Absent, n (%)	103 (100.0)
Present, n (%)	0
Week 4, n	101
Absent, n (%)	101 (100.0)
Present, n (%)	0
Week 20, n	93
Absent, n (%)	93 (100.0)
Present, n (%)	0
Week 36, n	90
Absent, n (%)	90 (100.0)
Present, n (%)	0
Week 52/early termination, n	100
Absent, n (%)	99 (99.0)
Present, n (%)	1 (1.0)
Week 53/early termination, n	78
Absent, n (%)	78 (100.0)
Present, n (%)	0
Generalized or Abdominal	
Baseline, n	103
Absent, n (%)	103 (100.0)
Present, n (%)	0
Week 4, n	101
Absent, n (%)	101 (100.0)
Present, n (%)	0
Week 20, n	93
Absent, n (%)	93 (100.0)
Present, n (%)	0
Week 36, n	90
Absent, n (%)	90 (100.0)
Present, n (%)	0
Week 52/early termination, n	100
Absent, n (%)	99 (99.0)
Present, n (%)	1 (1.0)
Week 53/early termination, n	78
Absent, n (%)	78 (100.0)
Present, n (%)	0

Baseline: The last assessment on or before Day 1 in this study.
N = total number of subjects; n = number of subjects in each subgroup.

DVT assessments are presented in the Table 13.

Table 13. Deep Vein Thrombosis Assessments - All Subjects

	N	None	Mild	Moderate	Severe
Baseline					
Localized pain	103	97 (94.2)	2 (1.9)	3 (2.9)	1 (1.0)
Localized tenderness	103	103 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
Swelling	103	97 (94.2)	4 (3.9)	2 (1.9)	0 (0.0)
Pitting edema	103	96 (93.2)	6 (5.8)	1 (1.0)	0 (0.0)
Collateral superficial veins (non-varicose)	103	103 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
Skin redness	103	103 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other	0	0 (-)	0 (-)	0 (-)	0 (-)
Week 4					
Localized pain	101	95 (94.1)	5 (5.0)	1 (1.0)	0 (0.0)
Localized tenderness	101	101 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
Swelling	101	96 (95.0)	3 (3.0)	2 (2.0)	0 (0.0)
Pitting edema	101	94 (93.1)	5 (5.0)	2 (2.0)	0 (0.0)
Collateral superficial veins (non-varicose)	101	101 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
Skin redness	101	101 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other	0	0 (-)	0 (-)	0 (-)	0 (-)
Week 20					
Localized pain	93	90 (96.8)	3 (3.2)	0 (0.0)	0 (0.0)
Localized tenderness	93	93 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
Swelling	93	88 (94.6)	3 (3.2)	2 (2.2)	0 (0.0)
Pitting edema	93	88 (94.6)	4 (4.3)	1 (1.1)	0 (0.0)
Collateral superficial veins (non-varicose)	93	93 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
Skin redness	93	92 (98.9)	1 (1.1)	0 (0.0)	0 (0.0)
Other	0	0 (-)	0 (-)	0 (-)	0 (-)
Week 36					
Localized pain	90	87 (96.7)	3 (3.3)	0 (0.0)	0 (0.0)
Localized tenderness	90	90 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
Swelling	90	85 (94.4)	4 (4.4)	1 (1.1)	0
Pitting edema	90	83 (92.2)	7 (7.8)	0 (0.0)	0 (0.0)
Collateral superficial veins (non-varicose)	90	90 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
Skin redness	90	90 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other	0	0 (-)	0 (-)	0 (-)	0 (-)
Week 52/early termination					
Localized pain	100	96 (96.0)	3 (3.0)	0 (0.0)	1 (1.0)
Localized tenderness	100	100 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
Swelling	100	93 (93.0)	7 (7.0)	0 (0.0)	0 (0.0)
Pitting edema	100	92 (92.0)	8 (8.0)	0 (0.0)	0 (0.0)
Collateral superficial veins (non-varicose)	100	100 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
Skin redness	100	100 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other	0	0 (-)	0 (-)	0 (-)	0 (-)
Week 53/early termination					
Localized pain	78	75 (96.2)	2 (2.6)	1 (1.3)	0 (0.0)
Localized tenderness	78	78 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
Swelling	78	73 (93.6)	5 (6.4)	0 (0.0)	0 (0.0)
Pitting edema	78	74 (94.9)	4 (5.1)	0 (0.0)	0 (0.0)
Collateral superficial veins (non-varicose)	78	78 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
Skin redness	78	78 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other	0	0 (-)	0 (-)	0 (-)	0 (-)

Baseline: The last assessment on or before Day 1 in this study.
N = total number of subjects.

None of the subjects showed visual field deterioration.

Summary of subjects with deterioration in neurological examination findings is presented in Table 14.

Table 14. Summary of Subjects With Deterioration in Neurological Examination Findings – All Subjects

		N=103		
		N*	%	N at Risk**
Cranial nerve function	Cranial nerve function	0	0	86
Mental state	Mental state	0	0	103
Coordination	Right finger to nose	0	0	88
	Left finger to nose	2	2.4	82
	Right finger tapping	1	1.3	77
	Left finger tapping	0	0	64
	Right rapid alternating hand movements	1	1.2	81
	Left rapid alternating hand movements	2	2.8	71
	Romberg test	1	1.5	65
Gait and station	Gait	1	1.4	71
Deep tendon reflexes	Right brachioradialis	1	1.4	72
	Left brachioradialis	1	1.5	67
	Right patellar	3	6.4	47
	Left patellar	3	7.5	40
	Right achilles	2	4.2	48
	Left achilles	3	6.7	45
Reflexes	Abnormal reflexes	1	1.9	53
Muscle strength	Right upper limb	1	1	99
	Left upper limb	2	2	98
	Right lower limb	1	1.2	81
	Left lower limb	2	2.5	80
Muscle tone	Right upper limb	1	1	103
	Left upper limb	1	1	102
	Right lower limb	5	4.9	102
	Left lower limb	5	4.9	102
Sensory function	Anesthesia	0	0	49
	Hypesthesia	1	4.5	22
	Allodynia	1	2.5	40
	Hyperalgesia	2	5.9	34

* N = subjects with an increase in intensity relative to the Baseline.
** N at risk = subjects who had the baseline examination findings considered as at risk.

Furthermore, there were 2 subjects with abnormal ECG finding at endpoint that was clinically significant. Of those, the significant ECG change from screening was observed in 1 subject. The atrial fibrillation in the subject was reported as an AE from abnormal ECG findings at the endpoint. The atrial fibrillation was mild in severity and resolved by a follow-up observation after the end of the treatment. The ECG results are presented in Table 15.

Table 15. ECG at Baseline and Last Observation - All Subjects

	N=103
Baseline, N	103
Normal, n (%)	80 (77.7)
Abnormal, not clinically significant, n (%)	22 (21.4)
Abnormal, clinically significant, n (%)	1 (1.0)
Unevaluable, n (%)	0 (0.0)
End of treatment, N	101
Normal, n (%)	77 (76.2)
Abnormal, not clinically significant, n (%)	22 (21.8)
Abnormal, clinically significant, n (%)	2 (2.0)
Unevaluable, n (%)	0 (0.0)

Baseline: The last assessment on or before Day 1 in this study.
ECG = electrocardiogram; N = number of subjects; n = number of subjects in each subgroup.

Major laboratory abnormalities (of which the incidence was 10% or higher, whether or not the baseline levels were within the reference range) were triglycerides increased, low density lipoprotein cholesterol levels raised, and urinary occult blood positive. There were no laboratory abnormalities reported as serious adverse events.

Sheehan-Suicidality Tracking Scale (Sheehan-STS): Sheehan-STS were summarized descriptively and no inferential testing was performed (Table 16).

Table 16. Summary of Sheehan-Suicidality Tracking Scale (C-CASA Categories) All Subjects

C-CASA Category Suicidal Ideation	N Assessed*	N=103
Screening	103	19 (18.4%)
Baseline	103	3 (2.9%)
Week 2	102	2 (2.0%)
Week 4	101	1 (1.0%)
Week 8	99	0 (0.0%)
Week 12	96	0 (0.0%)
Week 20	93	2 (2.2%)
Week 28	91	2 (2.2%)
Week 36	90	2 (2.2%)
Week 44	85	2 (2.4%)
Week 52/early termination	101	0 (0.0%)
Week 53/early termination	78	0 (0.0%)

* The number of subjects that were analyzed for the given endpoint.
C-CASA - Columbia Classification Algorithm of Suicide Assessment.
N = number of subjects.

CONCLUSIONS: This clinical trial was conducted to verify the safety and efficacy of the long-term use of pregabalin at doses up to 600 mg/day in subjects with central neuropathic pain (post spinal cord injury pain, post stroke pain, and multiple sclerosis pain).

Thirty-eight subjects with central neuropathic pain after spinal cord injury who had participated in the preceding study and shifted into this study; and 60 subjects with pain after cerebral stroke and 5 subjects with multiple sclerosis pain newly joined this study.

The median duration of pregabalin treatment was 367.0 days (ranging from 3 to 386 days).

At the endpoint of the interim reporting, the total SF-MPQ scores, sensory pain, affective pain showed an improvement from Baseline; suggesting a sustained analgesic effect of pregabalin long-term administration in subjects with central neuropathic pain. The mBPI-10 score also suggested an improvement from Baseline.

Treatment-emergent, treatment-related AEs were somnolence, weight increased, dizziness, and edema peripheral. Many of these events were either mild or moderate. Severe AEs occurred in 12 subjects (11.7%), of which 4 (3.9%) were determined treatment-related. SAEs were reported in 19 subjects (18.4%) as of 27 March 2012, and one of the SAEs occurred in 1 subject (1.0%) was determined treatment-related. Of these SAEs, femur fracture, recurrent cerebral infarction, arteriosclerosis coronary artery, and cerebral hemorrhage (1 event each) were unresolved. There were no deaths in this study. By these evidences, pregabalin was confirmed safe and well-tolerated, posing no significant clinical issues in this long-term study, and the types of AEs reported in this study were comparable to the known safety profile of pregabalin, and showed a sustained analgesic effect.