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

PROTOCOL NO.: A0081128

PROTOCOL TITLE: A Randomized Placebo-Controlled Trial of the Efficacy and Tolerability of Flexibly Dosed Pregabalin in the Treatment of Cancer-Induced Bone Pain

Study Centers: Thirty nine (39) centers took part in the study and randomized subjects: 1 each in Canada, Egypt, Finland, Italy, Spain, Thailand and Venezuela, 2 each in France, Mexico, Peru, Philippines and Sweden, 3 each in Republic of Korea, Russian Federation, Taiwan and the United States, 5 each in Hungary and Poland.

Study Initiation and Final Completion Dates: 20 December 2006 to 12 October 2010
The study was terminated prematurely.

Phase of Development: Phase 4

Study Objectives:

Primary: To assess the analgesic efficacy of flexibly dosed pregabalin compared with placebo, in the adjunctive treatment of subjects with cancer-induced bone pain as add-on therapy to standard-of-care opioids for moderate to severe pain due to bone metastases.

Secondary: To assess the safety and tolerability of pregabalin in the adjunctive treatment of subjects with cancer-induced bone pain.

METHODS

Study Design: This was a randomized, double-blind, flexible-dose, placebo-controlled, parallel-group, multicenter study.

The study consisted of a Screening Period (5 to 21 days), during which eligibility was ascertained and opioid stabilization was achieved; a double-blind treatment period comprising a dose adjustment period (lasting up to Day 14) and a dose maintenance period (lasting until Day 28); and a double-blind taper period (6 days).

Subjects meeting all eligibility criteria at the Screening Visit entered a screening/opioid stabilization period during which their dosage of opioids was stabilized, and daily diaries were completed (measuring worst pain at reference site, worst pain in general, and average pain over previous 24 hour period, and daily opioid use). Subjects meeting additional eligibility criteria at Visit 2 were eligible for randomization. All qualified subjects were

randomized to either pregabalin or matching placebo, and entered a dose-titration phase lasting up to Day 14. The doses of pregabalin or matching placebo were adjusted in a blinded manner to optimal dose and tolerability.

Following the end of the dose adjustment period (Day 14), subjects were to be at their optimized dose of pregabalin (100, 150, 300, or 600 mg/day) or placebo, and were to remain at this dose through Day 28 of the study, unless the dose was not well tolerated, in which case a single reduction in dose was permitted.

Daily diaries were completed from Screening until Day 28/early withdrawal (or screen failure). The schedule of activities is summarized in Table 1.

Table 1. Schedule of Activities

Phase	Double-Blind Treatment								
	Screening/Opioid Stabilization		Dose Adjustment			Dose Maintenance		Taper	Follow-Up
Clinic Visit	**V1**	**V2**	**Phone Contact**	**Phone Contact**	**Phone Contact**	**Phone Contact**	**Phone Contact**	**V3/ET[a]**	**Phone Contact[b]**
Study Day (+/- 3 days)	**-21 to -1[c]**	**0, 1**	**4, 5[c]**	**7,8[c]**	**10, 11[c]**	**14, 15[c]**	**21**	**28-34**	**35**
Assessments/Observations									
Obtain informed consent	X								
Inclusion/exclusion criteria	X	X							
Vital signs	X								
Height	X								
Weight, BP, pulse	X	X						X	
Demographics/medical history	X								
Prior analgesic medications	X								
Laboratory assessments	X							X	
12 lead ECG[d]	X								
Physical/neurological exam	X							X	
ECOG performance scale	X							X	
Subject assessment of worst pain	X								
Randomization		X							
Adverse events		X	X	X	X	X	X	X	X
Prior/concomitant medications	X	X	X	X	X	X	X	X	X
Prior/concomitant non-drug procedures/treatments	X	X	X	X	X	X	X	X	X
Dispense study drug		X						X	
Collect study drug accountability								X	X[b]
Study drug dose adjustment[e]			X[c]	X[c]	X[c]	X[c]			
Sustained release concomitant opioid medication	X	X	X	X	X	X	X	X	
Immediate release rescue opioid medication	X	X	X	X	X	X	X	X	
Subject disposition								X	
Dispense subject diary	X	X							
Collect subject diary		X						X	
Subject diary Daily worst pain (reference site) Daily worst pain (overall) Daily average pain Pain related sleep interference Total daily dose of pain medication	X	X	X	X	X	X	X	X	
Subject-Rated Measures									

Table 1. Schedule of Activities

Phase	Double-Blind Treatment								
	Screening/Opioid Stabilization		Dose Adjustment			Dose Maintenance		Taper	Follow-Up
Clinic Visit	**V1**	**V2**	**Phone Contact**	**Phone Contact**	**Phone Contact**	**Phone Contact**	**Phone Contact**	**V3/ET[a]**	**Phone Contact[b]**
Study Day (+/- 3 days)	**-21 to -1[c]**	**0, 1**	**4, 5[c]**	**7,8[c]**	**10, 11[c]**	**14, 15[c]**	**21**	**28-34**	**35**
Modified Brief Pain Inventory Short Form (mBPI-sf)		X						X	
Hospital Anxiety and Depression (HADS)		X						X	
Patient Global Impression of Change (PGIC)						X[e]		X	
Opioid-Related Symptom Distress Scale (OR SDS)		X				X[e]		X	
Modified Brief Fatigue Inventory (mBFI)		X						X	
Global Satisfaction with Current Pain Medications		X						X	
EuroQol (EQ-5D) Health State Profile		X						X	

BP = blood pressure; ECG = electrocardiogram; ECOG = Eastern Co-operative Oncology Group; ET = End of Treatment; V = visit.

a. When subject discontinued from trial at any time, or completed the maintenance phase, subject returned for a termination visit and entered the taper phase.
b. After completion of the taper phase, the subject returned study drug and its containers, either by mail or at the next visit to the physician. Clinic Visit was performed instead of telephone contact.
c. If subject's dose had been adjusted, the site staff called the subject the next study day to assess dose tolerability.
d. ECGs performed in the 30 days prior to screening were acceptable.
e. Completed in diary on Day 14.

Number of Subjects (Planned and Analyzed): The original sample size was 216 subjects (108 subjects per treatment group).

On 01 September 2010, following the conduct of a prespecified interim analysis, the Sponsor elected to terminate this study early.

Based on the results of an unblinded interim analysis conducted at 50% enrollment, it was determined that an increase in the number of subjects (from the original sample size of 216 subjects to the revised sample size of 356 subjects) enrolled in the study would be required in order to satisfy the statistical assumptions of the primary endpoint. However, the increase in the sample size would require a significant extension to the time period of enrollment. Due to the slow enrollment observed in the study, it was determined that it would be impractical to continue the study. The decision was not based on any concerns related to the safety of the study drug.

Subjects currently ongoing at that time were given the option to continue the study according to the study specified document. Subjects who elected to discontinue were to follow the study drug withdrawal plan according to the study specified document.

Of the 206 subjects who were screened, 152 were assigned to study treatment and received treatment: 72 subjects received pregabalin and 80 received placebo.

Diagnosis and Main Criteria for Inclusion: Male or female subjects ≥18 years of age with malignant, solid tumor that had been diagnosed as having metastasized to bone, and must had moderate to severe pain secondary to the bone metastasis at an identifiable reference site were enrolled into this trial. Subjects who had undergone diagnostic or therapeutic invasive interventions (angiography, biopsy, surgery) < 15 days prior to study start that would impact their assessment of pain at the reference pain site or area, in the opinion of the Investigator were excluded from the trial.

Study Treatment: Subjects who met all eligibility criteria were randomized to 1 of 2 treatment groups at Visit 2 (Day 0): pregabalin (flexible-dose 100-600 mg/day) or matching placebo capsules. Study drug was taken orally, twice a day, 1 capsule in the morning upon awakening and 1 capsule in the evening at bedtime. The medication could be taken with or without food.

Dosing began at 100 mg/day; all efforts were made to reach a minimum dose of 150 mg/day. Titration to a maximum dose ranging from 100-600 mg/day occurred until Day 14 of double-blind treatment, after which the dose was to be maintained until Day 28.

In subjects with creatinine clearance ≥60 mL/min, the maximum treatment dose was 600 mg/day and in subjects with creatinine clearance ≥30 mL/min and <60 mL/min, the maximum treatment dose was 300 mg/day.

Efficacy and Safety Endpoints:

Primary Endpoint: The primary efficacy endpoint was the change in the "worst pain" score from Baseline to the "worst pain" score during the fixed dose period at the reference site.

Secondary Endpoints: Safety and tolerability of pregabalin in the treatment of cancer-induced bone pain:

- Adverse event (AE) reporting;
- Serious adverse events (SAE);
- Subject disposition.

Safety Evaluations: AEs were monitored throughout the study. Laboratory assessments (serum hematology, biochemistry, and urinalysis) were obtained at Screening and the end of therapy. A physical exam was performed at the Screening and the end of therapy. Weight, blood pressure, and pulse were to be recorded at Screening, Baseline, and the end of therapy. Height was recorded at the Screening Visit.

Statistical Methods:

Analysis Sets: All safety analysis was performed using the safety population. All efficacy parameters were performed using the intent-to-treat (ITT) population. Primary efficacy parameter was analyzed additionally using the per protocol (PP) population.

Safety Population: All randomized subjects who were administered at least 1 dose of double-blind medication, and for whom at least 1 postbaseline safety evaluation was obtained were included in this population. Subjects were analyzed according to treatment they received.

Intent-to-Treat (ITT) Population: All subjects included in the safety population, and for whom at least 1 postbaseline efficacy evaluation was obtained were included in this population. Subjects were analyzed according to their randomized treatment assignment regardless of which treatment they actually were administered.

Per Protocol (PP) Population: All ITT subjects who were 80%-120% compliant on double-blind medication for all except at most 1 visit, without starting any prohibited medications or non-pharmacologic therapy, and were without other major protocol violations, were included in this population. Study violation criteria were defined before data base release and before unblinding of randomization code.

Due to early termination of the study, not all parameters prespecified in the study were analyzed and included here.

The primary efficacy parameter was the duration adjusted average change (DAAC) from baseline in the "daily worst pain at the reference site" (combined with "daily worst pain") on numeric rating scale (NRS) score during the fixed-dosing period, excluding taper phase. It was defined as area under the curve of change in worst pain after the subject had reached a stable pregabalin (placebo) dose divided by the corresponding treatment duration of each subject during the fixed-dosing period excluding the taper phase. The primary efficacy parameter was based on the NRS worst pain score collected from subject daily diary. Due to early termination of the study only descriptive analyses were performed.

Key secondary efficacy parameters were analyzed in the same manner as with the primary efficacy parameter.

The reporting of safety data were as per Sponsor safety standards.

RESULTS

Subject Disposition and Demography: Of the 72 subjects in the pregabalin group, 59 (81.9%) completed the study and 13 (18.1%) subjects discontinued the study early. None of the discontinuations were considered to be related to study drug. Of the 80 subjects in the placebo group, 59 (73.8%) completed the study and 21 (26.3%) subjects discontinued the study early. Two subjects discontinued due to AEs considered to be related to study drug. All other discontinuations were considered to be not related to study drug. A summary of subject disposition is presented in Table 2.

Table 2. Subject Disposition and Subjects Analyzed

Number (%) of Subjects	Pregabalin	Placebo
Screened=206		
Assigned to study treatment=152		
Treated	72	80
Completed	59 (81.9)	59 (73.8)
Discontinued	13 (18.1)	21 (26.3)
Subject died	3 (4.2)	4 (5.0)
Relation to study drug not defined	8 (11.1)	10 (12.5)
Insufficient clinical response	2 (2.8)	4 (5.0)
Other	2 (2.8)	2 (2.5)
Protocol violation	1 (1.4)	1 (1.3)
Withdrew consent	3 (4.2)	3 (3.8)
Related to study drug	0	2 (2.5)
Adverse event	0	2 (2.5)
Not related to study drug	2 (2.8)	5 (6.3)
Adverse event	2 (2.8)	5 (6.3)
Analyzed for safety		
Adverse events	72 (100.0)	80 (100.0)
Laboratory data	63 (87.5)	63 (78.8)

Discontinuations occurring outside the lag period have been attributed to the last study treatment received.

A summary of the demographic characteristics in the safety population is presented in Table 3.

Table 3. Demographic Characteristics

	Pregabalin			Placebo		
	Male	Female	Total	Male	Female	Total
Number (%) of subjects	36	36	72	39	41	80
Age (years)						
18-44	2 (5.6)	5 (13.9)	7 (9.7)	0	7 (17.1)	7 (8.8)
45-64	20 (55.6)	23 (63.9)	43 (59.7)	21 (53.8)	26 (63.4)	47 (58.8)
≥65	14 (38.9)	8 (22.2)	22 (30.6)	18 (46.2)	8 (19.5)	26 (32.5)
Mean	60.9	55.6	58.2	65.5	54.7	59.9
SD	12.1	9.9	11.3	9.4	11.6	11.9
Range	31-84	36-76	31-84	49-85	32-77	32-85
Race						
White	25 (69.4)	19 (52.8)	44 (61.1)	23 (59.0)	24 (58.5)	47 (58.8)
Black	2 (5.6)	0	2 (2.8)	1 (2.6)	1 (2.4)	2 (2.5)
Asian	7 (19.4)	10 (27.8)	17 (23.6)	7 (17.9)	12 (29.3)	19 (23.8)
Other	2 (5.6)	7 (19.4)	9 (12.5)	8 (20.5)	4 (9.8)	12 (15.0)
Weight (kg):						
Mean	72.2	61.9	67.1	72.1	64.4	68.1
SD	12.3	18.5	16.4	17.2	17.2	17.5
Range	37.2-95.0	38.9-123.0	37.2-123.0	42.0-118.0	34.0-110.0	34.0-118.0
N	36 (100.0)	36 (100.0)	72 (100.0)	39 (100.0)	41 (100.0)	80 (100.0)
Height (cm)						
Mean	172.0	158.8	165.4	168.0	158.8	163.3
SD	8.4	9.0	10.9	9.9	7.7	9.9
Range	154.0-186	141.5-176	141.5-186	146.0-183	143.0-175	143.0-183
N	36 (100.0)	36 (100.0)	72 (100.0)	39 (100.0)	41 (100.0)	80 (100.0)

N = number of subjects; SD = standard deviation.

Efficacy Results:

The primary efficacy parameter was the DAAC from Baseline in NRS score during the fixed-dosing period. The mean standard deviation (SD) DAAC in NRS worst pain scores for the fixed-dosing period was-1.53 (1.81) for the pregabalin group and -1.23 (1.74) for the placebo group.

A summary of the DAAC in NRS worst pain for the ITT population is presented in Table 4. The pregabalin group demonstrated a greater numerical decrease (ie, improvement) in the mean DAAC scores than the placebo group.

Table 4. Summary of DAAC in NRS Worst Pain – ITT Population

	Pregabalin (N=72)	Placebo (N=80)
Fixed-dosing period (Primary efficacy variable)		
N	72	77
Minimum	-7.89	-8.17
Median	-1.53	-0.79
Maximum	2.81	1.04
Mean (standard deviation)	-1.53 (1.81)	-1.23 (1.74)
14 days since fixed dose		
N	72	77
Minimum	-7.89	-8.08
Median	-1.43	-0.79
Maximum	2.81	1.04
Mean (standard deviation)	-1.47 (1.79)	-1.15 (1.72)
Flexible-dosing period		
N	69	76
Minimum	-4.47	-4.03
Median	-0.48	-0.36
Maximum	1.63	1.14
Mean (standard deviation)	-0.72 (1.11)	-0.53 (1.01)
Whole double-blind period		
N	72	77
Minimum	-6.40	-6.36
Median	-1.20	-0.80
Maximum	2.23	1.04
Mean (standard deviation)	-1.27 (1.45)	-1.03 (1.37)

For cohort subjects prior to study specified document amendment (where study visits were reduced) worst pain is considered while after this amendment worst pain at reference site was considered for cohort subjects.
Ordering of rows is determined by importance of endpoint.
Worst pain NRS scored 0-10 with 0 being "no pain" and 10 being "pain as bad as you can imagine".
DAAC = duration adjusted average change from Baseline, computed by area under the curve of each pain score by trapezoidal's rule, then divided by days in each period: ITT = intent-to-treat; N = number of subjects; NRS = Numeric Rating Scale.

A summary of the weekly mean scores of the NRS worst pain for the ITT population is presented in Table 5. The weekly mean SD scores were 4.52 (2.51) for the pregabalin group and 5.07 (2.33) for the placebo group at endpoint last observation carried forward (LOCF), and at each week of treatment, the mean weekly scores for the pregabalin group were lower (reduction in pain) than those of the placebo group.

Table 5. Summary of Weekly Mean of NRS Worst Pain - ITT Population

	Pregabalin (N=72)	Placebo (N=80)
Baseline		
N	72	79
Minimum	2.14	3.57
Median	6.14	6.14
Maximum	10.00	10.00
Mean (standard deviation)	6.28 (1.68)	6.47 (1.59)
Week 1		
N	72	78
Minimum	1.57	1.86
Median	5.43	6.29
Maximum	9.57	10.00
Mean (standard deviation)	5.51 (1.93)	6.05 (1.76)
Week 2		
N	70	73
Minimum	1.13	1.29
Median	5.00	5.57
Maximum	9.57	10.00
Mean (standard deviation)	5.09 (2.18)	5.53 (2.03)
Week 3		
N	67	69
Minimum	0.14	0.29
Median	4.00	5.14
Maximum	10.00	10.00
Mean (standard deviation)	4.61 (2.29)	5.09 (2.19)
Week 4		
N	64	63
Minimum	0.00	0.00
Median	3.86	5.00
Maximum	10.00	9.71
Mean (standard deviation)	4.23 (2.42)	4.76 (2.30)
LOCF		
N	72	78
Minimum	0.00	0.00
Median	4.00	5.00
Maximum	10.00	10.00
Mean (standard deviation)	4.52 (2.51)	5.07 (2.33)

For cohort subjects prior to study specified document amendment (where study visits were reduced) worst pain is considered while after this amendment worst pain at reference site was considered for cohort subjects.
Worst pain NRS scored 0-10 with 0 being "no pain" and 10 being "pain as bad as you can imagine".
ITT = intent-to-treat; N = number of subjects; NRS = Numeric Rating Scale; LOCF = last observation carried forward.

For the mean DAAC scores in NRS average pain, the pregabalin group had a greater decrease (ie, improvement) than the placebo group. The mean SD DAAC in NRS average pain scores for the fixed-dosing period was -1.24 (1.65) for the pregabalin group and -0.85 (1.59) for the placebo group.

At endpoint (LOCF), the weekly mean SD of the NRS average pain scores were 3.78 (2.20) for the pregabalin group and 4.42 (2.11) for the placebo group. For each week of treatment, the mean weekly scores for the pregabalin group were lower (indicating a reduction in pain) than the weekly mean scores for the placebo group.

A summary of the DAAC in NRS sleep interference score for the ITT population is presented in Table 6. The pregabalin group had a greater decrease (ie, improvement) in the mean

DAAC scores than the placebo group. The mean SD DAAC in NRS sleep interference scores for the fixed-dosing period was -1.37 (2.02) for the pregabalin group and -0.63 (1.78) for the placebo group.

Table 6. Summary of DAAC in NRS Sleep Interference Score – ITT Population

	Pregabalin (N=72)	Placebo (N=80)
Fixed-dosing period		
N	71	77
Minimum	-6.23	-7.24
Median	-0.93	-0.28
Maximum	5.01	4.19
Mean (standard deviation)	-1.37 (2.02)	-0.63 (1.78)
14 days since fixed dose		
N	71	77
Minimum	-6.18	-6.96
Median	-0.95	-0.26
Maximum	5.01	4.19
Mean (standard deviation)	-1.35 (1.98)	-0.55 (1.76)
Flexible-dosing period		
N	68	76
Minimum	-4.99	-3.30
Median	-0.71	-0.16
Maximum	1.82	4.19
Mean (standard deviation)	-0.76 (1.32)	-0.20 (1.12)
Whole double-blind period		
N	71	77
Minimum	-5.59	-5.79
Median	-0.87	-0.39
Maximum	3.57	4.19
Mean (standard deviation)	-1.18 (1.69)	-0.52 (1.47)

Duration adjusted average change from Baseline, computed by area under the curve of each pain score by trapezoidal rule, and then divided by days in each period.
Ordering of rows is determined by importance of endpoint.
Sleep interference NRS scored 0-10 with 0 being "does not interfere" and 10 being "completely interferes".
ITT = intent-to-treat; DAAC = duration adjusted average change; N = number of subjects; NRS = Numeric Rating Scale;

At endpoint (LOCF), the weekly mean SD of the NRS sleep interference scores were 2.97 (2.32) for the pregabalin group and 3.27 (2.50) for the placebo group. For each week of treatment, the mean weekly scores for the pregabalin group were lower (indicating less interference with sleep) than the weekly mean scores for the placebo group.

For all of the modified brief pain inventory-short form (mBPI-sf) scores (pain severity index, pain interference index, worst pain score, average pain score, and sleep interference), the pregabalin group demonstrated greater (ie, improvement) mean decreases from Baseline compared to the placebo group.

For both hospital anxiety and depression Scale subscale scores (anxiety and depression), the pregabalin group had slightly greater mean increases (indicating greater anxiety/depression) from Baseline compared to the placebo group.

A summary of the patient global impression of change (PGIC) score at Week 4 and at endpoint (LOCF) for the ITT population is presented in Table 7. At both time points, the pregabalin group had a lower mean PGIC score (ie, improvement) than the placebo group.

Table 7. Patient Global Impression of Change (PGIC) Score at Week 4 and at Endpoint - ITT Population

	Pregabalin (N=72)	Placebo (N=80)
Week 4		
N	59	60
Minimum	1.00	1.00
Maximum	7.00	7.00
Mean	2.73	2.87
Standard Deviation	1.39	1.46
LOCF		
N	69	74
Minimum	1.00	1.00
Maximum	7.00	7.00
Mean	2.88	2.99
Standard Deviation	1.46	1.45

1= very much improved; 2= much improved; 3= minimally improved; 4= no change; 5= minimally worse; 6= much worse; 7= very much worse.
Varying N across different visit weeks is primarily a result of study specified amendment document, in which subjects performed assessments only at Baseline and endpoint post study specified document amendment rather than weekly prior to protocol amendment.
ITT = intent-to-treat; LOCF = last observation carried forward; N = number of subjects.

For the frequency of PGIC scores, approximately two-thirds of subjects in both treatment groups had a score of 2 (much improved) or 3 (minimally improved) at Week 4 and at endpoint (LOCF).

Safety Results: A summary of treatment-emergent (all causality) and treatment-related AEs is presented in Table 8.

Fourteen subjects were reported to have experienced fatal treatment emergent adverse events (TEAEs), 6 (8.3%) in the pregabalin group and 8 (10.0%) in the placebo group. However, 13 subjects died during the study; 6 (8.3%) in the pregabalin group and 7 (8.8%) in the placebo group. One subject in the placebo group reported an AE thought to be fatal, but the subject was lost to follow-up and the death was not verified. None of the deaths was considered to be related to study drug.

Twenty-four subjects experienced serious adverse events, 12 (16.7%) in the pregabalin group and 12 (15.0%) in the placebo group. None was considered to be related to study drug. Discontinuations due to AEs were experienced by 3 (4.2%) subjects in the pregabalin group and 11 (13.8%) subjects in the placebo group.

Twenty-seven subjects (37.5%) experienced a total of 64 treatment-related TEAEs in the pregabalin group and 19 (23.8%) subjects experienced 44 TEAEs in the placebo group. No subjects experienced treatment-related SAEs.

Table 8. Treatment-Emergent (All Causalities) and Treatment-Related Adverse Events

Number (%) of subjects	All Causality		Treatment Related	
	Pregabalin	Placebo	Pregabalin	Placebo
Subjects evaluable for adverse events	72	80	72	80
Number of adverse events	177	158	64	44
Subjects with adverse events	48 (66.7)	48 (60.0)	27 (37.5)	19 (23.8)
Subjects with serious adverse events	12 (16.7)	12 (15.0)	0	0
Subjects with Severe or life-threatening adverse events	19 (26.4)	14 (17.5)	7 (9.7)	1 (1.3)
Subjects with fatal adverse events	6 (8.3)	8 (10.0)[a]	0	0
Subjects discontinued due to adverse events	3 (4.2)	11 (13.8)	0	2 (2.5)
Subjects with dose reduced due to adverse events	7 (9.7)	5 (6.3)	6 (8.3)	5 (6.3)
Subjects with temporary discontinuation due to adverse events	2 (2.8)	4 (5.0)	0	3 (3.8)

Except for the number of adverse events subjects were counted only once per treatment in each row.
Serious adverse events - according to the Investigator's assessment.
MedDRA (version 13.1) coding dictionary applied.
MedDRA = Medical Dictionary for Regulatory Activities.
a. One adverse event in the placebo group was considered to be a fatal event, but the subject was lost to follow-up and death was not verified. Seven subjects in the placebo group were known to have died during the study.

Forty-eight subjects (66.7%) experienced a total of 177 TEAEs in the pregabalin group and 48 (60.0%) subjects experienced 158 TEAEs in the placebo group. A summary of the TEAEs that occurred in ≥5% of subjects in any treatment group, regardless of causality, is presented in Table 9. The most common TEAEs were somnolence (25.0% in the pregabalin group and 7.5% in the placebo group), dizziness (15.3% in the pregabalin group and 8.8% in the placebo group), fatigue (11.1% in the pregabalin group and 5.0% in the placebo group), and nausea (9.7% in the pregabalin and 12.5% in the placebo group).

Table 9. Treatment-Emergent Adverse Events ≥5% of Subjects in any Treatment Group (All Causalities)

Number (%) of Subjects with Adverse Events by System Organ Class and MedDRA Preferred Term	Pregabalin n (%)	Placebo n (%)
Number of subjects (%)		
Evaluable for adverse events	72	80
With adverse events	48 (66.7)	48 (60.0)
Discontinued due to adverse events	3 (4.2)	11 (13.8)
Ear and labyrinth disorders	4 (5.6)	1 (1.3)
Vertigo	4 (5.6)	0
Gastrointestinal disorders	22 (30.6)	20 (25.0)
Diarrhoea	5 (6.9)	3 (3.8)
Nausea	7 (9.7)	10 (12.5)
Vomiting	6 (8.3)	4 (5.0)
General disorders and administration site conditions	19 (26.4)	14 (17.5)
Disease progression	4 (5.6)	3 (3.8)
Fatigue	8 (11.1)	4 (5.0)
Oedema peripheral	4 (5.6)	3 (3.8)
Musculoskeletal and connective tissue disorders	10 (13.9)	8 (10.0)
Arthralgia	4 (5.6)	2 (2.5)
Bone pain	0	4 (5.0)
Nervous system disorders	28 (38.9)	19 (23.8)
Disturbance in attention	4 (5.6)	0
Dizziness	11 (15.3)	7 (8.8)
Headache	4 (5.6)	2 (2.5)
Somnolence	18 (25.0)	6 (7.5)
Tremor	5 (6.9)	2 (2.5)
Renal and urinary disorders	3 (4.2)	6 (7.5)
Dysuria	0	4 (5.0)
Respiratory, thoracic and mediastinal disorders	9 (12.5)	8 (10.0)
Cough	1 (1.4)	4 (5.0)
Dyspnoea	7 (9.7)	3 (3.8)

AEs and SAEs are not separated out.
Subjects were only counted once per treatment for each row.
Includes data up to 999 days after last dose of study drug.
MedDRA (v13.1) coding dictionary applied.
AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; n = number of subjects with specified criteria; SAE = serious adverse event; v = version.

A summary of treatment-related TEAEs by SOC and preferred term is presented in Table 10. In general, the most common TEAEs considered to be treatment-related were the same as most common TEAEs regardless of causality.

Table 10. Treatment-Emergent Adverse Events in any Treatment Group (Treatment-Related)

Number (%) of Subjects with Adverse Events by System Organ Class and MedDRA Preferred Term	Pregabalin n (%)	Placebo n (%)
Number (%) of Subjects:		
Evaluable for adverse events	72	80
With adverse events	27 (37.5)	19 (23.8)
Discontinued due to adverse events	-	2 (2.5)
Cardiac disorders	0	2 (2.5)
Tachycardia	0	2 (2.5)
Ear and labyrinth disorders	2 (2.8)	0
Vertigo	2 (2.8)	0
Eye disorders	1 (1.4)	1 (1.3)
Accommodation disorder	1 (1.4)	0
Eyelid oedema	0	1 (1.3)
Gastrointestinal disorders	9 (12.5)	7 (8.8)
Abdominal pain upper	1 (1.4)	2 (2.5)
Constipation	1 (1.4)	1 (1.3)
Diarrhoea	2 (2.8)	1 (1.3)
Dry mouth	1 (1.4)	1 (1.3)
Nausea	2 (2.8)	2 (2.5)
Vomiting	2 (2.8)	2 (2.5)
General disorders and administration site conditions	6 (8.3)	4 (5.0)
Axillary pain	0	1 (1.3)
Chest discomfort	0	2 (2.5)
Fatigue	4 (5.6)	1 (1.3)
Oedema peripheral	2 (2.8)	1 (1.3)
Temperature intolerance	0	1 (1.3)
Infections and infestations	0	1 (1.3)
Rash pustular	0	1 (1.3)
Injury, poisoning and procedural complications	1 (1.4)	1 (1.3)
Facial bones fracture	0	1 (1.3)
Fall	1 (1.4)	0
Investigations	1 (1.4)	1 (1.3)
Blood creatinine	1 (1.4)	0
Heart rate increased	0	1 (1.3)
Musculoskeletal and connective tissue disorders	3 (4.2)	2 (2.5)
Arthralgia	1 (1.4)	1 (1.3)
Bone pain	0	1 (1.3)
Muscle spasms	2 (2.8)	0
Nervous system disorders	22 (30.6)	12 (15.0)
Ataxia	1 (1.4)	0
Disturbance in attention	3 (4.2)	0
Dizziness	9 (12.5)	3 (3.8)
Dyskinesia	1 (1.4)	0
Headache	1 (1.4)	1 (1.3)
Hypoaesthesia	1 (1.4)	1 (1.3)
Lethargy	0	1 (1.3)
Memory impairment	1 (1.4)	0
Monoplegia	1 (1.4)	0
Myoclonus	0	1 (1.3)
Neuralgia	0	1 (1.3)
Paraesthesia	1 (1.4)	0
Sensory disturbance	0	1 (1.3)
Somnolence	14 (19.4)	5 (6.3)
Tremor	3 (4.2)	1 (1.3)
Psychiatric disorders	1 (1.4)	3 (3.8)
Anxiety	0	1 (1.3)
Delusion	1 (1.4)	0
Disorientation	1 (1.4)	0

Table 10. Treatment-Emergent Adverse Events in any Treatment Group (Treatment-Related)

Number (%) of Subjects with Adverse Events by System Organ Class and MedDRA Preferred Term	Pregabalin n (%)	Placebo n (%)
Insomnia	0	1 (1.3)
Panic attack	0	1 (1.3)
Renal and urinary disorders	2 (2.8)	1 (1.3)
Bladder spasm	1 (1.4)	0
Dysuria	0	1 (1.3)
Urinary retention	1 (1.4)	0
Respiratory, thoracic and mediastinal disorders	1 (1.4)	1 (1.3)
Cough	0	1 (1.3)
Dyspnoea	1 (1.4)	0
Skin and subcutaneous tissue disorders	0	1 (1.3)
Rash	0	1 (1.3)

AEs and SAEs are not separated out.
Subjects were only counted once per treatment for each row.
Includes data up to 999 days after last dose of study drug.
MedDRA (v13.1) coding dictionary applied.
AEs = adverse events; MedDRA = Medical Dictionary for Regulatory Activities; n = number of subjects in the specified category; SAEs = serious adverse events; v = version.

Serious Adverse Events: A list of the subjects who experienced SAEs is presented in Table 11. Twenty-four subjects experienced SAEs, 12 (16.7%) in the pregabalin group and 12 (15.0%) in the placebo group. In addition, 1 subject in each group had an SAE before randomization. Six subjects experienced SAEs during the screening period, but were not randomized to treatment and did not receive study drug. No subjects experienced SAEs deemed related to treatment.

Table 11. Serious Adverse Events

Serial No.	Sex/Age	MedDRA Preferred Term	Onset Day	Severity	Relationship
Pre-Randomization					
1	N/A	Disease progression	N/A	N/A	N/A
2	N/A	Disease progression	N/A	N/A	N/A
3	N/A	Pyrexia	N/A	N/A	N/A
4	N/A	Disease progression	N/A	N/A	N/A
5	N/A	Malignant neoplasm progression	N/A	N/A	N/A
6	N/A	Accidental death	N/A	N/A	N/A
Pregabalin					
7	M/31 yrs	Deep vein thrombosis	14	Severe	Not related
8	F/76 yrs	Pneumonia	43	Severe	Not related
		Back pain	43	Severe	Not related
9	F/51 yrs	Disease progression	27	Fatal	Not related
		Cerebral infarction	13	Severe	Not related
10	M/51 yrs	Disease progression	28	Fatal	Not related
11	M/69 yrs	Disease progression	13	Fatal	Not related
12	F/38 yrs	Neutropenic infection	-10	Severe	N/A
13	M/64 yrs	Device dislocation	24	Severe	Not related
14	F/36 yrs	Anemia	34	Mild	Not related
		Lower respiratory tract infection	34	Mild	Not related
		Dyspnea	34	Moderate	Not related
15	F/61 yrs	Anemia	13	Severe	Not related
		Pneumonia	14	Severe	Not related
		Tonsillitis	12	Severe	Not related
16	M/46 yrs	Renal failure acute	18	Life-threatening	Not related
		Renal failure acute	27	Life-threatening	Not related
17	M/79 yrs	Disease progression	32	Fatal	Not related
18	M/75 yrs	Disease progression	36	Fatal	Not related
19	M/84 yrs	Disease progression	10	Fatal	Not related
Placebo					
20	F/74 yrs	Disease progression	3	Life-threatening	Not related
		Disease progression	6	Fatal	Not related
21	M/49 yrs	Disease progression	51	Fatal	Not related
22	F/56 yrs	Dyspnea	1	Severe	Not related
23[a]	F/65 yrs	Femur fracture	11	Fatal	Not related
24	F/43 yrs	Device related infection	20	Mild	Not related
		Bone pain	52	Moderate	Not related
25	M/60 yrs	Disease progression	27	Fatal	Not related
		Pneumonia	25	Fatal	Not related
		Cough	25	Mild	Not related
		Hemoptysis	25	Severe	Not related
26	M/60 yrs	Metabolic disorder	29	Fatal	Not related
		Prostate cancer	22	Fatal	Not related
27	M/73 yrs	Anemia	28	Severe	Not related
		Gastrointestinal hemorrhage	28	Severe	Not related
		Dehydration	28	Severe	Not related
		Renal failure	28	Life-threatening	Not related
		Cardiac arrest	30	Fatal	Not related
28	F/54 yrs	Anemia	-7	--	N/A
		Pleural effusion	-2	--	N/A
		Anemia	-5	Severe	N/A
		Pleural effusion	0	Severe	Not related
		Myocardial infarction	5	Life-threatening	Not related
		Pericardial effusion	5	Fatal	Not related
		Metastases to pleura	5	Severe	Not related
29	F/52 yrs	Tachycardia	32	Severe	Not related
		Malaise	32	Severe	Not related
		Pyrexia	32	Severe	Not related
30	M/82 yrs	Humerus fracture	14	Severe	Not related

Table 11. Serious Adverse Events

Serial No.	Sex/Age	MedDRA Preferred Term	Onset Day	Severity	Relationship
		Septic shock	29	Life-Threatening	Not related
		Septic shock	29	Fatal	Not related
31	F/47 yrs	Spinal cord compression	14	Moderate	Not related

Age at Screening.
Onset Day relative to start of study treatment. First day of study treatment = Day 1.
MedDRA (v13.1) coding dictionary applied.
F = female; M = male; MedDRA = Medical Dictionary for Regulatory Activities; N/A = not applicable; No. = number; yrs = years.
a. The serious event was considered to be fatal, but the subject was lost to follow-up and the death was not verified.

Permanent Discontinuations due to Adverse Events: A list of the 14 subjects (3 in the pregabalin group and 11 in the placebo group) who discontinued the study due to an AE is presented in Table 12.

Table 12. Subject Discontinuations due to Adverse Events

Serial No.	Sex/Age	MedDRA Preferred Term	Onset Day	Severity	Relationship
Pregabalin					
1[a]	F/51 yrs	Disease Progression	27	Fatal	Not related
2	M/46 yrs	Renal failure acute	18	Life-threatening	Not related
		Renal failure acute	27	Life-threatening	Not related
3	M/84 yrs	Performance status decreased	8	Life-threatening	Not related
Placebo					
4	F/74 yrs	Disease progression	6	Fatal	Not related
5	F/43 yrs	Thrombocytopenia	2	Life-threatening	Not related
6[b]	F/65 yrs	Femur fracture	11	Fatal	Not related
7	F/55 yrs	Tachycardia	5	Moderate	Related
		Chest discomfort	5	Moderate	Related
		Fatigue	5	Moderate	Related
		Heart rate increased	5	Moderate	Related
8	F/34 yrs	Tachycardia	8	Mild	Related
		Vomiting	8	Mild	Related
		Coughing	8	Mild	Related
9[a]	M/73 yrs	Cardiac arrest	30	Fatal	Not related
10	M/60 yrs	Metastases to central nervous system	9	Severe	Not related
11[a]	M/82 yrs	Septic shock	29	Fatal	Not related
12	M/62 yrs	Performance status decreased	4	Moderate	Not related
		Malignant neoplasm progression	4	Moderate	Not related
13[c]	M/56 yrs	Nausea	44	Mild	Not related
14	M/57 yrs	Bone pain	13	Severe	Not related

Age at Screening.
Onset Day relative to start of study treatment. First day of study treatment = Day 1.
MedDRA (v13.1) coding dictionary applied.
F = female; M = male; MedDRA = Medical Dictionary for Regulatory Activities; No. = number; yrs = years.
a. Subject was listed as discontinuing due to death.
b. The subject discontinued due to an adverse event considered to be fatal, but the subject was lost to follow-up and the death was not verified.
c. Subject was listed as completing the study. The event was reported during the follow-up telephone contact.

Dose Reductions or Temporary Discontinuations due to Adverse Events: Nine subjects in the pregabalin group had a dose reduction (7 subjects, 9.7%) or temporary discontinuation (2 subjects, 2.8%) due to AEs. Nine subjects in the placebo group had a dose reduction (5 subjects, 6.3%) or temporary discontinuation (4 subjects, 5.0%) due to AEs. Dose reduction or temporary discontinuation due to AEs is presented in Table 13.

Table 13. Temporary Discontinuations or Dose Reductions due to Adverse Events

Serial No.	Sex/Age	MedDRA Preferred Term	Onset Day	Severity	Relationship
Pregabalin					
1	F/51 yrs	Dyspnea	16	Mild	Not related
2	F/59 yrs	Chill	5	Mild	Not related
3	M/64 yrs	Fatigue	12	Moderate	Related
4	F/61 yrs	Tremor	13	Moderate	Related
5	F/36 yrs	Disturbance in attention	16	Mild	Related
		Somnolence	16	Mild	Related
6	M/70 yrs	Somnolence	12	Severe	Related
7	F/54 yrs	Fatigue	14	Severe	Related
		Somnolence	13	Severe	Related
8	F/49 yrs	Dizziness	8	Severe	Related
9	M/75 yrs	Vertigo	19	Mild	Not related
		Somnolence	18	Mild	Not related
Placebo					
10	F/45 yrs	Dyspepsia	-3	Mild	Not related
11	F/65 yrs	Somnolence	9	Mild	Related
12	F/34 yrs	Tachycardia	3	Moderate	Related
		Diarrhea	3	Mild	Related
		Vomiting	3	Mild	Related
		Chest discomfort	3	Mild	Related
		Sensory disturbance	3	Mild	Related
13	M/60 yrs	Panic attack	17	Moderate	Related
		Panic attack	24	Severe	Related
14	F/46 yrs	Somnolence	5	Moderate	Related
15	F/47 yrs	Abdominal pain upper	7	Moderate	Related
16	F/58 yrs	Nausea	20	Mild	Related
		Somnolence	20	Mild	Related
17	M/69 yrs	Temperature intolerance	14	Mild	Related
18	M/82 yrs	Humerus fracture	14	Severe	Not related
		Tremor	6	Mild	Related
		Insomnia	7	Mild	Related
19	M/80 yrs	Rash pustular	12	Mild	Related

Age at Screening.
Onset Day relative to start of study treatment. First day of study treatment = Day 1.
MedDRA (v13.1) coding dictionary applied.
F = female; M = male; MedDRA = Medical Dictionary for Regulatory Activities; No. = number; yrs = years.

Deaths: A total of 13 subjects died during the study; 6 (8.3%) in the pregabalin group and 7 (8.8%) in the placebo group (Table 14). In addition, 5 subjects who were not randomized to treatment and did not receive study drug, died. None of the deaths was considered to be related to study drug.

Table 14. Deaths

Serial No.	Sex/Age	MedDRA Preferred Term	Onset Day	Severity	Relationship
Pre-Randomization					
1	N/A	Disease progression	N/A	N/A	N/A
2	N/A	Disease progression	N/A	N/A	N/A
3	N/A	Disease progression	N/A	N/A	N/A
4	N/A	Malignant neoplasm progression	N/A	N/A	N/A
5	N/A	Accidental death	N/A	N/A	N/A
Pregabalin					
6	F/51 yrs	Disease progression	27	Fatal	Not related
7	M/51 yrs	Disease progression	28	Fatal	Not related
8	M/69 yrs	Disease progression	13	Fatal	Not related
9	M/79 yrs	Disease progression	32	Fatal	Not related
10	M/75 yrs	Disease progression	36	Fatal	Not related
11	M/84 yrs	Disease progression	10	Fatal	Not related
Placebo					
12	F/74 yrs	Disease progression	3	Life-threatening	Not related
		Disease progression	6	Fatal	Not related
13	M/49 yrs	Disease progression	51	Fatal	Not related
14	M/60 yrs	Disease progression	27	Life-threatening	Not related
		Pneumonia	25	Fatal	Not related
15	M/60 yrs	Metabolic disorder	29	Fatal	Not related
		Prostate cancer	22	Fatal	Not related
16	M/73 yrs	Cardiac arrest	30	Fatal	Not related
17	F/54 yrs	Metastases to pleura	5	Severe	Not related
18	M/82 yrs	Septic shock	29	Life-threatening	Not related
		Septic shock	29	Fatal	Not related

Age at Screening.
Onset Day relative to start of study treatment. First day of study treatment = Day 1.
MedDRA (v13.1) coding dictionary applied.
F = female; MedDRA = Medical Dictionary for Regulatory Activities; M = male; No. = number; N/A = not applicable; yrs = years.

Laboratory Evaluations: In general, the incidence of laboratory abnormalities was similar between treatment groups. The median changes in both treatment groups were small and not clinically significant.

For vital signs, the mean changes in both treatment groups were small and not clinically significant. The percentage of subjects with an increase of ≥30 mm Hg in systolic blood pressure or an increase of ≥20 mm Hg in diastolic blood pressure was slightly higher for the placebo group than for the pregabalin group (6.1% to 9.1% compared to 3.1% to 8.2%, respectively).

CONCLUSION: As the result of an unblinded interim analysis, the study was terminated due to time considerations for enrollment. There were no safety concerns noted.