PFIZER INC.

These results are supplied for informational purposes only.
Prescribing decisions should be made based on the approved package insert.

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

PROTOCOL NO: A0081124

PROTOCOL TITLE: A Randomized, Double-Blind, Placebo-Controlled Trial of the Prevention and Treatment of Chemotherapy-Induced Peripheral Neuropathy Symptoms With Pregabalin in Subjects With Advanced Colorectal Cancer

Study Centers: A total of 15 centers took part in the study and randomized subjects; 2 each in Australia, Italy and Taiwan, 3 each in Germany Spain and the Republic of Korea.

Study Initiation Date and Final Completion Date: 04 January 2007 to 10 March 2008. The study was terminated prematurely.

Phase of Development: Phase 4

Study Objectives:

Primary Objective:

- To evaluate the efficacy of pregabalin compared to placebo in subjects with paresthesic positive symptoms of chemotherapy-induced neuropathy using the duration adjusted average change (DAAC) of paresthesia from the onset of chemotherapy (Last observation carried forward [LOCF]).

The persistent paresthesic positive symptoms were measured by a numeric rating scale (NRS) modified to assess paresthesia rather than pain.

Secondary Objectives:

- To evaluate the parasthesic, dysesthesic, and pain symptoms score over each chemotherapy cycle.
- To evaluate the proportion of subjects experiencing positive neuropathic symptoms in each treatment group at endpoint.
- To evaluate the subject's pain interference of function as measured by the modified Brief Pain Inventory Short Form (mBPI-SF).
- To evaluate the effect of pregabalin on sleep interference in subjects with chemotherapy-induced peripheral neuropathy, as measured by the Daily Sleep Interference Scale.

- To evaluate the effect of pregabalin on self-reported symptoms of depression and anxiety in subjects with chemotherapy induced peripheral neuropathy as measured by the Hospital Anxiety and Depression Scale (HADS).

- To evaluate the subject's overall health status as measured by the Euro Quality of Life (EQ-5D) Health State Profile Questionnaire.

- To validate the NRS on paresthesia, dysesthesia and pain symptoms.

- To evaluate the time to onset of any paresthesic positive symptoms of the chemotherapy-induced neuropathy from the onset of chemotherapy.

- To evaluate the time to onset of persistent paresthesic, dysesthesic and pain positive symptoms of chemotherapy-induced neuropathy from time of initial chemotherapy, as measured using the modified NRS.

- To evaluate the time to onset of acute positive neuropathic symptoms (paresthesia, dysesthesia and pain) as defined in the background section of the chemotherapy-induced neuropathy from time of initial chemotherapy to the last cycle.

- To evaluate the time to onset of the chemotherapy-induced cold intolerance developed from time of initial chemotherapy to the last cycle.

Safety:

- To evaluate the safety and tolerability of pregabalin for the treatment of subjects with pain associated with chemotherapy-induced neuropathy.

- To evaluate the percentage of subjects who require dose reduction or discontinue chemotherapy.

METHODS:

Study Design: This was a randomized, double-blind, placebo-controlled pregabalin study in subjects with advanced colorectal cancer and about to undergo chemotherapy with oxaliplatin combined with 5-fluorouracil/folinic acid (5-FU/FA).

Subjects entered an 18-week, double-blind treatment phase with 1 week taper.

At Visit 1, all Screening assessments were completed by the Investigator.

At Visit 2, subjects were randomized in a double-blind fashion (in a 1:1 ratio) to receive either pregabalin 75 mg twice daily (BID) or matching placebo. All subjects were instructed to take their first dose of pregabalin approximately 90 minutes before their first chemotherapy cycle. Subjects then started their first chemotherapy infusion cycle with the recommended dosage of oxaliplatin and 5-FU/FA 85 mg/m^2. Each infusion cycle consisted of an oxaliplatin dose infusion combined with 5-FU/FA repeated every 2 weeks at each study visit.

At the end of the first chemotherapy cycle and in the absence of dose limiting side effects, the double-blind treatment with pregabalin or placebo was adjusted upward to 150 mg twice daily

(BID) in Cycle 2 (Visit 3). The neuropathic pain symptom inventory (NPSI) was used by the Investigator to assess if the dose was to be titrated up to a maximum total daily dose of pregabalin 300 mg BID or down to a minimum of pregabalin 75 mg BID at each subsequent cycle. This dose titration was done to maximize tolerability and maintain efficacy. During the study, only 1 dose reduction was allowed for each subject. If multiple dose reductions occurred, the subject discontinued from the study (this did not apply to the taper study drug regime).

Subjects returned to the study site for efficacy and safety assessments prior to each infusion Cycles 1 to 9 (Visits 2 to 10). A subject was considered to have completed the study if he/she had 9 cycles of chemotherapy and all efficacy and safety assessments. All subjects who completed the study or terminated prematurely underwent an end-of-study drug taper over a 1-week period and returned for a final visit after 1 week. Table 1 summarizes the schedule of activities.

Table 1. Schedule of Activities

Procedures	**Study Phase**											
Study Week/Day	**Screening Week (-1)**	**Baseline (Cycle 1)**	**Cycle 2**	**Cycle 3**	**Cycle 4**	**Cycle 5**	**Cycle 6**	**Cycle 7**	**Cycle 8**	**Cycle 9 or Last Cycle**	**End of Study - Taper**	**Follow-Up**
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
	[-7 ± 3]	**[0]**	**[14 ± 6]**	**[28 ± 6]**	**[42 ± 6]**	**[56 ± 6]**	**[70 ± 6]**	**[84 ± 6]**	**[98 ± 6]**	**[112 ± 6]**	**[126 ± 6]**	**[133 ± 3]**
Assessments/observations												
Informed consent	X											
Demographics	X											
Inclusion/exclusion criteria	X											
Medical history	X	X										
Vital signs/weight[a]	X	X	X	X	X	X	X	X	X	X	X	X
Prior and concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X
Prior and concomitant non-drug treatments and procedures	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination	X										X	
Laboratory collections	X	X	X	X	X	X	X	X	X	X	X	
Serum pregnancy test	X											
12-Lead electrocardiogram[b]	X											
Investigator rated assessments												
ECOG performance status	X	X	X	X	X	X	X	X	X	X	X	
Quantitative assessments of neuropathic pain	X											
Subject completed questionnaires												
Numerical rating scale (daily)[c,d]	X	X	X	X	X	X	X	X	X	X	X	
Sleep interference scale (daily)[d]	X	X	X	X	X	X	X	X	X	X	X	
Neuropathic pain symptom inventory[c]	X	X	X	X	X	X	X	X	X	X	X	

Table 1. Schedule of Activities

Modified brief pain inventory - short form (MBPI-SF)		X	X	X	X	X	X	X	X	X	X	
Hospital anxiety and depression scale		X	X	X	X	X	X	X	X	X	X	
EuroQol (EQ-5D) health state profile questionnaire											X	
Study medication dispensing												
Study medication dispensed[e]		X	X	X	X	X	X	X	X	X		
Randomization[e]		X										
Dose adjustment[e]			X	X	X	X	X	X	X	X		
Taper[e]											X	
Subject disposition form[e]												X
Principal Investigator declaration												X

ECOG = eastern cooperative oncology group.

a. Height was collected at Screening visit.
b. Electrocardiograms performed in the 30 days prior to Screening were acceptable.
c. Numeric rating scale – paresthesia, dysesthesia, and pain were to be given with the neuropathic pain symptom inventory before each chemotherapy cycle.
d. Collected and reviewed subject diaries at each visit.
e. Impala visited (subject identity number assigned, randomized, medication dispensed, status marked) drug accountability completed (as applicable).

Number of Subjects (Planned and Analyzed): Approximately 300 subjects were planned for screening in order to achieve 200 evaluable subjects (100 subjects per treatment arm). A total of 69 subjects were screened, of which 64 subjects were randomized and 61 subjects received treatment: 32 subjects received pregabalin and 29 subjects received placebo.

Diagnosis and Main Criteria for Inclusion: Male or female subjects aged 18-80 years with a diagnosis of cytological confirmed carcinoma of the Colon Stage III (Dukes C) or metastatic Colorectal Cancer (Dukes D). Subject had decided to receive standard of care for the treatment of cancer with oxaliplatin combined with 5-FU/FA for a minimum of 9 cycles.

Exclusion Criteria: Subjects were excluded if they had presence of neuropathic pain or peripheral polyneuropathy or identified causes of paiful paresthesia including radiotherapy-induced or malignant plexopathy, lumbar or cervical radiculopathy prior to Baseline. Any subjects who were not suitable to be treated with either Oxaliplatin and/or 5-FU/FA or pregabalin according to the respective local labeling.

Study Treatment: Pregabalin and matching placebo were supplied as grey-colored capsules by the sponsor. Subjects entered an 18-week, double-blind treatment phase with 1 week taper.

During the double-blind treatment phase, subjects were randomized in a 1:1 ratio to receive pregabalin 150 to 600 mg/day flexible dose + chemotherapy or matching placebo + chemotherapy. The study drug was taken orally BID with or without food, once in the morning and once at night starting with the first chemotherapy infusion. The first dose of study drug was taken approximately 90 minutes before their first chemotherapy cycle. The possible dose levels of pregabalin were 150 mg/day (75 mg capsules BID), 300 mg/day (150 mg capsules BID) or 600 mg/day (300 mg capsules BID). At Cycle 1, all eligible subjects were randomized to either pregabalin 75 mg BID (150 mg/day) capsules or matching placebo. At Cycle 2, in the absence of dose-limiting adverse events (AEs), the daily dose of pregabalin/placebo was increased to 150 mg BID (300 mg/day). At subsequent visits the dose was either increased or decreased in a step wise fashion based on the subject's clinical response and tolerability (e.g, 300 mg/day to 600 mg/day; 300 mg/day to 150 mg/day).

All subjects who completed the study or terminated prematurely underwent a 1-week end-of-study medication taper. The study drug was taken BID and was tapered to a lower dose for 7 days depending on the dose received during the double-blind treatment period. This was followed by a 1-week observation period.

Efficacy and Safety Endpoints:

Primary Endpoint:

- DAAC of paresthesia from the onset of chemotherapy (LOCF) using a modified NRS scale.

Secondary Endpoints:

- The severity of parasthesic, dysesthesic, and pain symptom scores over each chemotherapy cycle.
- The proportion of subjects experiencing positive neuropathic symptoms in each treatment group at endpoint.
- Change in subject's pain interference of function from baseline to endpoint as measured by the mBPI-SF.
- Change in sleep interference in subjects with chemotherapy-induced peripheral neuropathy from baseline to endpoint as measured by the sleep interference scale.
- Change in self-reported symptoms of depression and anxiety in subjects with chemotherapy induced peripheral neuropathy from baseline to endpoint as measured by HADS.
- Subject's overall health status as measured by EQ-5D Health State Profile Questionnaire at endpoint.
- The time to onset of any paresthesic positive symptoms of the chemotherapy-induced neuropathy from the onset of chemotherapy.
- The time to onset of persistent dysesthesic and pain positive symptoms of chemotherapy-induced neuropathy from time of initial chemotherapy, as measured using the modified NRS.
- The time to onset of acute positive neuropathic symptoms (paresthesia, dysesthesia and pain) of the chemotherapy-induced neuropathy from time of initial chemotherapy.
- The time to onset of the chemotherapy-induced cold intolerance developed from time of initial chemotherapy.

Safety Endpoints**:**

- Safety and tolerability of pregabalin for the treatment of subjects with pain associated with chemotherapy-induced neuropathy.
- Percentage of subjects who require dose reduction or discontinue chemotherapy.

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

Statistical Methods:

- Safety Population**:** included all randomized subjects who were administered at least 1 dose of double blind medication, and for whom at least 1 post-baseline safety evaluation was obtained. Subjects were analyzed according to the treatment they received.

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

- Per Protocol (PP)**:** 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.

A protocol amendment was issued as a result of a blinded interim analysis, in which the primary assumption was not met. The primary endpoint was modified as a result, and an unblinded analysis conducted. Due to early termination of the study, not all parameters were analyzed and included.

The primary analysis was the comparison of DAAC for a period of 10 days of paresthesia scores from the onset of chemotherapy to the last cycle (LOCF) between pregabalin and placebo groups, using an analysis of covariance (ANCOVA) model with model terms of treatment, study center and baseline score. Paresthesia score was measured by a NRS modified to assess paresthesia rather than pain.

The secondary efficacy parameters were analyzed either by an ANCOVA model with model terms of treatment, study centre, and baseline score, if baseline score was available or by an ANOVA model with the same main effects as above.

The safety summaries and listings were as per sponsor safety standards.

RESULTS:

Subject Disposition and Demography: Of the 69 screened subjects, 64 subjects were randomized and 61 subjects received treatment (32 received pregabalin and 29 received placebo). A total of 38 subjects (19 receiving pregabalin and 19 placebo) completed the study. Subject disposition is summarized in Table 2.

Table 2. Subject Evaluation Group

	Pregabalin	Placebo
Number of subjects		
Assigned to study treatment 64		
Treated[a]	32 (100.0)	29 (100.0)
Completed	19 (59.4)	19 (65.5)
Discontinued	13 (40.6)	10 (34.5)
Death (not related to study drug)	1 (3.1)	1[b] (0)
Related to study drug	3 (9.4)	2 (6.9)
Adverse event	3 (9.4)	2 (6.9)
Not related to study drug	9 (28.1)	8 (27.6)
Adverse event	4 (12.5)	5 (17.2)
Other	3 (9.4)	2 (6.9)
Subject no longer willing to participate in study	2 (6.3)	1 (3.4)
Analyzed for safety		
Adverse events	32 (100.0)	29 (100.0)
Laboratory data	31 (96.9)[c]	29 (100.0)

a. Three subjects were randomized but did not receive study medication.
b. Subject died 3 weeks after discontinuation.
c. One subject receiving pregabalin was not analyzed for laboratory data.

Table 3 summarizes the demographic characteristics in the safety population. There were more male subjects than female subjects in both treatment groups (65.6% and 72.4% in pregabalin and placebo groups, respectively). The mean age was 58.9 years for the pregabalin treated subject group and 56.1 years for the placebo treated subject group.

Table 3. Demographic Characteristics

Number of Subjects	Pregabalin (N=32)	Placebo (N=29)
Gender		
Male, n(%)	21 (65.6)	21 (72.4)
Female, n(%)	11 (34.4)	8 (27.6)
Age (years)		
Mean (SD)	58.9 (11.3)	56.1 (12.9)
Range	24-78	25-73
Race		
White, n(%)	18 (56.3)	15 (51.7)
Black, n(%)	1 (3.1)	0
Asian, n(%)	13 (40.6)	14 (48.3)

N =number of subjects for each treatment group; n = number of subjects in the specified category;
SD = standard deviation.

Efficacy Results:

Primary Endpoint Results:

Table 4 summarizes the DAAC from baseline of paresthesic symptom score at each chemotherapy cycle as well as at LOCF endpoint cycle as measured by NRS in the ITT population. No statistically significant differences were noted between treatment groups at any cycle.

Table 4. DAAC From Baseline of Paresthesic Symptom Score Within Each Cycle as Measured by NRS-ITT Population

Day	Treatment	N	n	LS Mean (SE)	LS Mean Difference (SE)	p-Value
Cycle 1	Pregabalin	32	25	0.03 (0.06)	-0.09 (0.08)	0.2536
	Placebo	29	27	0.13 (0.05)		
Cycle 2	Pregabalin	32	26	0.35 (0.16)	0.13 (0.23)	0.5757
	Placebo	29	26	0.22 (0.16)		
Cycle 3	Pregabalin	32	24	0.53 (0.21)	0.15 (0.30)	0.6065
	Placebo	29	23	0.37 (0.21)		
Cycle 4	Pregabalin	32	25	0.64 (0.21)	0.24 (0.31)	0.4301
	Placebo	29	23	0.40 (0.22)		
Cycle 5	Pregabalin	32	24	1.03 (0.33)	0.50 (0.49)	0.3125
	Placebo	29	22	0.53 (0.35)		
Cycle 6	Pregabalin	32	21	0.74 (0.28)	0.09 (0.41)	0.8169
	Placebo	29	21	0.64 (0.28)		
Cycle 7	Pregabalin	32	17	0.93 (0.30)	-0.03 (0.40)	0.9359
	Placebo	29	22	0.96 (0.26)		
Cycle 8	Pregabalin	32	16	0.83 (0.29)	-0.20 (0.40)	0.6233
	Placebo	29	19	1.03 (0.27)		
Cycle 9	Pregabalin	32	16	0.92 (0.36)	-0.73 (0.50)	0.1569
	Placebo	29	18	1.65 (0.34)		
LOCF endpoint	Pregabalin	32	26	1.11 (0.35)	-0.16 (0.49)	0.7489
	Placebo	29	27	1.27 (0.34)		

DAAC = duration adjusted average change; ITT = intent to treat; LS = least squares; LOCF = Last observation carried forward; N = number of subjects for each treatment group; NRS = numeric rating scale; n = number of subjects with data for analysis for each treatment group; SE = standard error.

Secondary Endpoint Results:

Table 5 summarizes the DAAC from baseline of dysesthesic symptom score at chemotherapy Cycle 9 and LOCF endpoint cycle as measured by NRS in the ITT population. There were no significant differences between treatment groups at cycles presented below or at earlier cycles.

Table 5. DAAC From Baseline of Dysesthesic Symptom Score Within Each Cycle as Measured by NRS-ITT Population

Day	Treatment	N	n	LS Mean (SE)	LS Mean Difference (SE)
Cycle 9	Pregabalin	32	16	1.24 (0.44)	-0.51 (0.62)
	Placebo	29	18	1.75 (0.42)	
LOCF endpoint	Pregabalin	32	26	1.36 (0.38)	0.02 (0.54)
	Placebo	29	27	1.33 (0.38)	

DAAC = duration adjusted average change; ITT = intent to treat; LS = least squares; LOCF = Last observation carried forward; N = number of subjects for each treatment group; NRS = numeric rating scale; n = number of subjects with data for analysis for each treatment group; SE = standard error.

Table 6 summarizes the DAAC from baseline of pain symptom score at chemotherapy Cycle 9 and LOCF endpoint cycle as measured by NRS in the ITT population. There were no significant differences at cycles presented below or at earlier cycles.

Table 6. DAAC From Baseline of Pain Symptom Score Within Each Cycle as Measured by NRS-ITT Population

Day	Treatment	N	n	LS Mean (SE)	LS Mean Difference (SE)
Cycle 9	Pregabalin	32	16	0.86 (0.41)	-0.11 (0.58)
	Placebo	29	18	0.97 (0.39)	
LOCF Endpoint	Pregabalin	32	26	0.65 (0.27)	-0.13 (0.39)
	Placebo	29	27	0.78 (0.27)	

DAAC = duration adjusted average change; ITT = intent to treat; LS = least squares; LOCF = Last observation carried forward; N =number of subjects for each treatment group; NRS = numeric rating scale; n = number of subjects with data for analysis for each treatment group; SE = standard error.

Table 7 summarizes the change from baseline in burning spontaneous pain, pressing spontaneous pain, paroxysmal pain, evoked pain, and paresthesia/dysesthesia and in total NPSI at chemotherapy Cycle 9 and LOCF endpoint cycle in the ITT population.

Generally, there were no significant differences between treatment groups for all parameters at each cycle. However, the treatment difference between pregabalin and placebo in the paresthesia/dysesthesia pain subscale was significant in favor of placebo at Cycle 2 (difference = 0.25, p=0.0416, 95% CI: 0.01, 0.50) and at Cycle 4 (difference = 0.37, p=0.0331, 95% CI: 0.03, 0.70).

Table 7. Change From Baseline in NPSI Subscales at Each Cycle-ITT Population

Day	Treatment	N	n	LS Mean (SE)	LS Mean Difference (SE)
Burning Spontaneous Pain					
Cycle 9	Pregabalin	32	19	0.54 (0.28)	-0.05 (0.39)
	Placebo	29	20	0.59 (0.27)	
LOCF endpoint	Pregabalin	32	29	0.33 (0.18)	-0.01 (0.26)
	Placebo	29	27	0.35 (0.19)	
Pressing Spontaneous Pain					
Cycle 9	Pregabalin	32	19	0.25 (0.09)	0.10 (0.12)
	Placebo	29	20	0.14 (0.08)	
LOCF endpoint	Pregabalin	32	29	0.15 (0.06)	0.07 (0.09)
	Placebo	29	27	0.08 (0.06)	
Paroxysmal Pain					
Cycle 9	Pregabalin	32	18	0.18 (0.17)	-0.20 (0.24)
	Placebo	29	20	0.38 (0.16)	
LOCF endpoint	Pregabalin	32	28	0.11 (0.10)	-0.10 (0.15)
	Placebo	29	27	0.20 (0.11)	
Evoke Pain					
Cycle 9	Pregabalin	32	19	0.74 (0.26)	0.15 (0.37)
	Placebo	29	20	0.59 (0.26)	
LOCF endpoint	Pregabalin	32	29	0.46 (0.18)	0.02 (0.27)
	Placebo	29	27	0.43 (0.19)	
Paresthesia/Dysesthesia Pain					
Cycle 9	Pregabalin	32	18	1.17 (0.36)	0.32 (0.49)
	Placebo	29	20	0.85 (0.34)	
LOCF endpoint	Pregabalin	32	29	0.83 (0.24)	0.31 (0.34)
	Placebo	29	27	0.52 (0.25)	
Total Score					
Cycle 9	Pregabalin	32	17	0.03 (0.01)	0.00 (0.01)
	Placebo	29	20	0.03 (0.01)	
LOCF endpoint	Pregabalin	32	28	0.02 (0.01)	0.00 (0.01)
	Placebo	29	27	0.02 (0.01)	

ITT = intent to treat; LS = least squares; LOCF = Last observation carried forward; NPSI = Neuropathic pain symptom inventory; N =number of subjects for each treatment group; n = number of subjects with data for analysis for each treatment group; SE = standard error.

Table 8 summarizes the time to onset of persistent paresthesic positive symptoms of chemotherapy-induced neuropathy in the ITT population.

Table 8. Time to Onset of Persistent Paresthesic Positive Symptoms of Chemotherapy-Induced Neuropathy-ITT Population

Symptom Score	Treatment	N	n	Kaplan-Meier Estimated Probability of Event at Cycle								
				1	2	3	4	5	6	7	8	9
≥1	Pregabalin	30	10		0.033	0.067	0.100	0.233		0.268	0.305	0.343
	Placebo	29	9		0.034	0.070	0.106	0.142	0.213	0.249	0.285	0.321
≥2	Pregabalin	30	7			0.033	0.100	0.200			0.236	
	Placebo	29	6					0.036	0.071		0.143	0.214
≥3	Pregabalin	30	4			0.033	0.067	0.100	0.135			
	Placebo	29	3						0.071		0.107	
≥4	Pregabalin	30	3			0.033		0.100				
	Placebo	29	3						0.071			0.107

ITT = intent to treat; N = number of subjects for each treatment group; n = number of subjects with event.

Table 9 summarizes the time to onset of any persistent paresthesia, dysesthesia and pain positive symptoms of chemotherapy-induced neuropathy in the ITT population.

Table 9. Time to Onset of any Persistent Paresthesia, Dysesthesia and Pain Positive Symptoms of Chemotherapy-Induced Neuropathy -ITT Population

Symptom Score	Treatment	N	n	Kaplan-Meier Estimated Probability of Event at Cycle								
				1	2	3	4	5	6	7	8	9
≥1	Pregabalin	30	14		0.067	0.167	0.200	0.267		0.371		0.489
	Placebo	29	10		0.069	0.141		0.212	0.284		0.320	0.355
≥2	Pregabalin	30	8		0.067	0.100	0.133	0.200			0.273	
	Placebo	29	8			0.036		0.071	0.143		0.179	0.286
≥3	Pregabalin	30	5		0.033	0.067	0.100	0.167				
	Placebo	29	4			0.036		0.071	0.107		0.143	
≥4	Pregabalin	30	3			0.033		0.100				
	Placebo	29	4			0.036			0.107			0.143

ITT = intent to treat; N = number of subjects for each treatment group; n = number of subjects with event.

Table 10 summarizes the proportion of subjects experiencing persistent paresthesic, dysesthesic and pain symptoms at the chemotherapy Cycle 9 and LOCF endpoint cycle in the ITT population.

Table 10. Proportion of Subjects Experiencing Persistent Paresthesic, Dysesthesic and Pain Symptoms Through all Cycles-ITT Population

Symptom Score	Day	Treatment	Persistent Paresthesic		Persistent Dysesthesic		Persistent Pain	
			N	n (%)	N	n (%)	N	n (%)
≥1	Cycle 9	Pregabalin	19	7 (36.84)	19	10 (52.63)	19	6 (31.58)
		Placebo	19	6 (31.58)	19	4 (21.05)	19	2 (10.53)
	LOCF endpoint	Pregabalin	30	8 (26.67)	30	11 (36.67)	30	6 (20.00)
		Placebo	29	7 (24.14)	29	5 (17.24)	29	3 (10.34)
≥2	Cycle 9	Pregabalin	19	4 (21.05)	19	5 (26.32)	19	2 (10.53)
		Placebo	19	3 (15.79)	19	3 (15.79)	19	1 (5.26)
	LOCF endpoint	Pregabalin	30	5 (16.67)	30	6 (20.00)	30	2 (6.67)
		Placebo	29	3 (10.34)	29	4 (13.79)	29	2 (6.90)
≥3	Cycle 9	Pregabalin	19	2 (10.53)	19	3 (15.79)	19	1 (5.26)
		Placebo	19	1 (5.26)	19	1 (5.26)	19	1 (5.26)
	LOCF endpoint	Pregabalin	30	3 (10.00)	30	4 (13.33)	30	1 (3.33)
		Placebo	29	1 (3.45)	29	2 (6.90)	29	2 (6.90)
≥4	Cycle 9	Pregabalin	19	1 (5.26)	19	1 (5.26)	19	0 (0.00)
		Placebo	19	1 (5.26)	19	1 (5.26)	19	1 (5.26)
	LOCF endpoint	Pregabalin	30	2(6.67)	30	2 (6.67)	30	0 (0.00)
		Placebo	29	1 (3.45)	29	2 (6.90)	29	2 (6.90)

LOCF = last observation carried forward; ITT = intent to treat; N = number of subjects for each treatment group; n = number of subjects with event.

Safety Results:

Thirty-one subjects reported a total of 225 treatment emergent adverse events (TEAEs) in the pregabalin treatment group and 29 subjects reported 229 TEAEs in the placebo treatment group. A summary of all causality AEs is presented in Table 11. Nausea and anorexia were the most frequently reported TEAE in both the treatment groups. No subject had an AE of suicide, suicide attempt or ideation.

Table 11. Overview of All Causality Adverse Events

	Pregabalin (N=32)	Placebo (N=29)
Number of adverse events	225	229
Subjects with adverse events	31 (96.9)	29 (100.0)
Subjects with serious adverse events	5 (15.6)	7 (24.1)
Subjects with Grade 3 or 4 adverse event	12 (37.5)	10 (34.5)
Subjects who discontinued due to adverse events	6 (18.8)[a]	8 (27.6)
Subjects with dose reduced or temporary discontinuation due to adverse events	3 (9.4)	2 (6.9)

AEs/SAEs are not separated out.

a. In addition to these 6 subjects, 1 subject also discontinued due to an unspecified adverse event.

TEAEs (all causality): Grade 2 AEs (all cycles) were the most frequently reported all-causality AEs in subjects receiving pregabalin (11 subjects [34.4%]) and placebo (15 subjects [51.7%]). Grade 1 AEs (all cycles) were the most frequently reported treatment-related AEs in subjects receiving pregabalin (6 subjects [18.8%]). Grade 2 AEs (all cycles) were the most frequently reported treatment-related AEs in subjects receiving

placebo (6 subjects [20.7%]). Nausea and anorexia were the most frequently reported TEAE in both the treatment groups (Table 12).

Table 12. Incidence of Treatment-Emergent All Causality Adverse Events (All Cycles) Reported by ≥2 Subjects in any Grade

Adverse Event Preferred Term (%)	Pregabalin				Placebo			
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 1	Grade 2	Grade 3	Grade 4
Nausea	9 (28.1)	6 (18.8)	1 (3.1)	0	7 (24.1)	5 (17.2)	1 (3.4)	0
Anorexia	10 (31.3)	3 (9.4)	0	0	7 (24.1)	4 (13.8)	0	1 (3.4)
Diarrhea	4 (12.5)	5 (15.6)	0	0	4 (13.8)	3 (10.3)	1 (3.4)	0
Pyrexia	4 (12.5)	4 (12.5)	1 (3.1)	0	4 (13.8)	1 (3.4)	0	0
Neutropenia	2 (6.3)	1 (3.1)	2 (6.3)	4 (12.5)	2 (6.9)	3 (10.3)	4 (13.8)	1 (3.4)
Constipation	6 (18.8)	2 (6.3)	0	0	6 (20.7)	2 (6.9)	0	0
Fatigue	7 (21.9)	1 (3.1)	0	0	5 (17.2)	2 (6.9)	0	0
Thrombocytopenia	2 (6.3)	3 (9.4)	2 (6.3)	0	5 (17.2)	2 (6.9)	1 (3.4)	0
Asthenia	4 (12.5)	3 (9.4)	0	0	2 (6.9)	2 (6.9)	0	0
Dizziness	6 (18.8)	1 (3.1)	0	0	4 (13.8)	0	0	0
Neuropathy Peripheral	7 (21.9)	0	0	0	5 (17.2)	2 (6.9)	0	0
Mucosal Inflammation	5 (15.6)	0	1 (3.1)	0	3 (10.3)	2 (6.9)	0	0
Alopecia	6 (18.8)	0	0	0	4 (13.8)	0	0	0
Leukopenia	1 (3.1)	1 (3.1)	3 (9.4)	0	3 (10.3)	2 (6.9)	3 (10.3)	0
Vomiting	3 (9.4)	1 (3.1)	1 (3.1)	0	4 (13.8)	6 (20.7)	0	0
Headache	1 (3.1)	3 (9.4)	1 (3.1)	0	2 (6.9)	0	0	0
Chills	3 (9.4)	1 (3.1)	0	0	1 (3.4)	1 (3.4)	0	0
Anemia	1 (3.1)	1 (3.1)	0	1 (3.1)	0	2 (6.9)	0	0
Peripheral Sensory Neuropathy	3 (9.4)	0	0	0	3 (10.3)	0	0	0
Dyspnea	2 (6.3)	0	0	1 (3.1)	1 (3.4)	0	0	0
Palmar-plantar erythrodysaesthesia syndrome	3 (9.4)	0	0	0	4 (13.8)	0	0	0
Stomatitis	3 (9.4)	0	0	0	3 (10.3)	2 (6.9)	0	0
Nasopharyngitis	2 (6.3)	0	0	0	4 (13.8)	0	0	0
Urinary Tract Infection	0	2 (6.3)	0	0	0	0	0	0
Drug Hypersensitivity	1 (3.1)	1 (3.1)	0	0	1 (3.4)	2 (6.9)	0	0
Hypoesthesia	2 (6.3)	0	0	0	2 (6.9)	0	0	0
Cough	2 (6.3)	0	0	0	4 (13.8)	0	0	0
Pruritus	2 (6.3)	0	0	0	2 (6.9)	1 (3.4)	0	0
Rash	2 (6.3)	0	0	0	3 (10.3)	1 (3.4)	0	0
Phlebitis	2 (6.3)	0	0	0	1 (3.4)	0	0	0
Insomnia	1 (3.1)	1 (3.1)	0	0	2 (6.9)	3 (10.3)	0	0
Abdominal Pain	0	1 (3.1)	0	0	5 (17.2)	0	0	0
Gastritis	1 (3.1)	0	0	0	2 (6.9)	0	0	0
Hepatic Function Abnormal	1 (3.1)	0	0	0	2 (6.9)	0	0	0
Hypokalemia	0	0	1 (3.1)	0	2 (6.9)	0	0	0
Paresthesia	0	1 (3.1)	0	0	3 (10.3)	1 (3.4)	0	0
Peripheral Coldness	0	0	0	0	2 (6.9)	0	0	0
Weight Increased	0	0	0	0	0	1 (3.4)	2 (6.9)	0
Polyneuropathy	0	0	0	0	2 (6.9)	0	0	0

A summary of treatment related AEs is presented in Table 13 The most common treatment-related AEs were dizziness, headache, asthenia, fatigue, weight increased and polyneuropathy.

Table 13. Incidence of Treatment-Related Adverse Events (All Cycles)

Preferred Term	Pregabalin				Placebo			
(%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 1	Grade 2	Grade 3	Grade 4
Dizziness	3 (9.4)	1 (3.1)	0	0	2 (6.9)	0	0	0
Headache	0	1 (3.1)	1 (3.1)	0	0	0	0	0
Asthenia	1 (3.1)	1 (3.1)	0	0	0	1 (3.4)	0	0
Fatigue	2 (6.3)	0	0	0	1 (3.4)	0	0	0
Weight increased	0	0	0	0	0	1 (3.4)	2 (6.9)	0
Polyneuropathy	0	0	0	0	2 (6.9)	0	0	0
Anorexia	0	0	0	0	0	1 (3.4)	0	0
Neutropenia	0	0	0	1 (3.1)	0	0	0	0
Constipation	1 (3.1)	0	0	0	1 (3.4)	0	0	0
Thrombocytopenia	0	0	0	0	1 (3.4)	0	0	0
Leukopenia	0	0	1 (3.1)	0	0	1 (3.4)	0	0
Drug hypersensitivity	0	1 (3.1)	0	0	0	1 (3.4)	0	0
Insomnia	0	0	0	0	0	1 (3.4)	0	0
Gastritis	1 (3.1)	0	0	0	0	0	0	0
Paresthesia	0	0	0	0	1 (3.4)	0	0	0
Vertigo	0	1 (3.1)	0	0	0	0	1 (3.4)	0
Edema peripheral	1 (3.1)	0	0	0	0	0	0	0
Pain	0	0	0	0	1 (3.4)	0	0	0
ALT increased	0	0	0	0	0	1 (3.4)	0	0
AST increased	0	0	0	0	0	1 (3.4)	0	0
Amnesia	1 (3.1)	0	0	0	0	0	0	0
Syncope vasovagal	0	0	1 (3.1)	0	0	0	0	0

AE/SAE results are not separated out.
ALT = alanine aminotransferase; AST = aspartate aminotransferase.

Twenty-six subjects reported a total of 119 TEAEs (considered background [chemotherapy] related) in the pregabalin treatment group and 19 subjects reported 106 TEAEs (considered background related) in the placebo treatment group. Table 14 summarizes the TEAEs related to the background treatment.

Table 14. Treatment-Emergent Adverse Events Considered Background Related

	Pregabalin	Placebo
Subjects evaluable for adverse events	32	29
Number of adverse events	119	106
Subjects with adverse events	26	19
Subjects with serious adverse events	1	2
Subjects with Grade 3 or 4 adverse event	8	5
Subjects who discontinued due to adverse events	4	0
Subjects with temporary discontinuation due to adverse events	1	1

Treatment emergent serious adverse events all causality are summarized in Table 15. A total of 5 subjects receiving pregabalin and 7 subjects receiving placebo reported SAEs. None of the SAEs were considered related to treatment by the Investigator and the Sponsor.

Table 15. Incidence of Treatment-Emergent All Causality Serious Adverse Events

S.No.	MedDRA Preferred Term	Treatment Phase	Dose	Start/Stop Day	Grade/Outcome
Pregabalin					
1	Dyspneaa	Active	600 mg	121/121	4/Resolved[a]
2	Extravasation	Active	150 mg	1/19	3/Resolved
3	Nausea	Active	600 mg	76/80	3/Resolved
	Vomiting	Active	600 mg	76/80	3/Resolved
	Dehydration	Active	600 mg	77/80	3/Resolved
4	Arrhythmia	Active	600 mg	94/102	2/Resolved
	Anorexia	Active	600 mg	94/140	2/Resolved
	Dehydration	Active	600 mg	94/98	2/Resolved
	Pulmonary Embolism	Active	600 mg	94/119	1/Resolved
5	Small Intestinal Obstruction	Active	300 mg	79/86	4/Resolved
	Pyrexia	Active	300 mg	65/69	2/Resolved
Placebo					
6	Bacterial Infection	Active	0 mg	10/43	2/Resolved
	Pleural Effusion[b]	Active	0 mg	-5/1	2/Resolved
7	Pyrexia	Active	0 mg	3/4	1/Resolved
	Pyrexia	Active	0 mg	127/132	2/Resolved
8	Ileus Paralytic	Active	0 mg	96/97	4/Resolved
	Nausea	Active	0 mg	88/114	3/Resolved
	Pneumonia	Active	0 mg	92/114	2/Resolved
	Anorexia	Active	0 mg	88/114	4/Resolved
	Shock	Active	0 mg	96/99	4/Resolved
9	Leukopenia	Active	0 mg	113/[>114]	2/Still Present
	Thrombocytopenia	Active	0 mg	113/119	2/Resolved
10	Catheter site Hemorrhage	Active	0 mg	0/9	4/Resolved
	Disease Progression[c]	Active	0 mg	100/122	-/Resolved
11	Metastases to Liver	Active	0 mg	26/[>29]	3/Still Present
	Peritoneal Carcinoma	Active	0 mg	26/[>29]	3/Still Present
12	Vitreous Hemorrhage	Active	0 mg	81/[>99]	2/Still Present

Values in brackets [ ] were imputed from incomplete dates and times
MedDRA = medical dictionary for regulatory activities; SAE = serious adverse event; S.No. = serial number.
a. Subject died following an SAE of dyspnea.
b. Non treatment-emergent.
c. Subject died due to disease progression 3 weeks after discontinuation.

Permanent Discontinuations: Seven subjects in the pregabalin treatment group and 8 subjects in the placebo treatment group permanently discontinued treatment due to AEs. Table 16 summarizes the subject discontinuations due to AEs.

Table 16. Subject Discontinuations due to Adverse Events

S.No.	Treatment Phase	Relationship to Study Drug	Adverse Event
Pregabalin			
1	Active	Related	Vertigo
2	Active	Related	Drug hypersensitivity
3[a]	Active	Related	Unspecified
4	Active	Not related	Neutropenia
5	Active	Not related	Neutropenia
6	Active	Not related	Nausea
7	Active	Not related	Allergic reaction
Placebo			
1	Active	Related	Alanine aminotransferase and aspartate aminotransferase increased
2	Active	Related	Drug hypersensitivity
3	Active	Not related	Bacteria infection
4	Active	Not related	Fever
5	Active	Not related	Paralytic ileus
6	Active	Not related	Progressive disease
7	Active	Not related	Hepatic metastases and peritoneal carcinosis
8[b]	Active	Not related	Vitreous hemorrhage

AE = adverse event; S.No. = serial number.

a. Subject had AE discontinued marked on final status but had no AEs on the case report form with corresponding action of AE discontinued. The subject had suffered from small intestinal obstruction that resolved 6 days before he was discontinued.

b. Subject had 'no longer willing to participate in the study for final status, but had the AE of vitreal hemorrhage on AE page with action of discontinued.

Three subjects receiving pregabalin had dose reduction or temporary discontinuation due to AEs. One subject stopped temporarily due to treatment-related dizziness, 1 due to small intestinal obstruction and 1 due to diarrhea. Two subjects receiving placebo had dose reduction or temporary discontinuation due to AEs. One subject stopped temporarily due to treatment-related increased alanine aminotransferase and increased aspartate aminotransferase and 1 subject stopped temporarily due to nausea, pneumonia, anorexia, dehydration and shock, all unrelated to treatment.

Deaths: There were a total of 2 deaths. One subject in the pregabalin treatment group died following an SAE of dyspnea (Grade 4), which was considered unrelated to treatment by the Investigator. One subject in the placebo treatment group died due to disease progression 3 weeks after discontinuation.

CONCLUSIONS:

As a result of the lack of symptom emergence, enrollment was halted, and the endpoint modified. The design of this study was altered due to the fact that the primary assumptions upon which it was powered (emergence of symptomatology) were not met. The study was then terminated when the interim analysis showed that the conditional power to detect a difference in treatment groups was insufficient to warrant study continuation. There were no safety concerns noted.