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

PROTOCOL NO.: A0081269

PROTOCOL TITLE: A Phase 3B Multi-Center, Double-Blind, Randomized, Placebo-Controlled, Cross-Over Efficacy and Safety Study of Pregabalin in the Treatment of Patients With Painful Diabetic Peripheral Neuropathy and Pain on Walking

Study Center: Subjects were randomized at 36 centers in the following 4 countries: United States (25), Sweden (4), South Africa (4), and Czech Republic (3). In addition, there were 11 centers that received study drug but did not randomize subjects.

Study Initiation and Completion Dates: 19 December 2011 to 02 July 2013.

Phase of Development: Phase 3b

Study Objectives: There were two co-primary objectives for this study in subjects with painful diabetic peripheral neuropathy (DPN) to evaluate the efficacy of pregabalin compared to placebo in:

- The reduction in DPN pain; and
- The reduction in DPN pain on walking.

In addition, the study assessed if pregabalin provided other benefits associated with improved functional outcomes (secondary objectives). The safety and tolerability of pregabalin were also evaluated.

METHODS

Study Design: This study was a randomized, double-blind, placebo-controlled, multi-center, 2-period cross-over study in subjects with painful DPN and pain on walking (Table 1, Figure 1). Subjects with conditions other than DPN that could cause pain on walking were excluded. Subjects were initially screened for eligibility. Subjects were asked to complete a daily pain and sleep diary on the telephone using interactive voice recognition system (IVRS) starting at Visit 1/Screening and continuing through the Visit 12/Follow-up. Subjects with a mean pain score of at least 4 (moderate to severe pain) and who met the pain on walking criteria (postwalk pain score of at least 4, and greater than the pre-walk pain score at Visit 1/Screening and Visit 2/Baseline) were randomized to double-blind treatment.

In each of the two double-blind treatment periods, subjects received either pregabalin followed by placebo (Sequence 1) or placebo followed by pregabalin (Sequence 2). The

duration of each treatment period was 6 weeks (2-week dose titration and 4-week fixed dose), with a 2-week single-blind washout (blinded to subject) between treatment periods. A 1-week taper was administered at the end of the second treatment period, followed by a final Follow-Up Visit. In each double-blind treatment period, those subjects randomized to pregabalin received a total daily dose of 150 mg/day administered as 50 mg 3 times a day (TID) by mouth for the first week and a total daily dose of 300 mg/day administered as 100 mg TID for the second week. Once on 300 mg/day, one dose reduction was allowed based on tolerability. At the end of the second week, the dose was fixed at the optimized dose for the following 4 weeks.

Figure 1. Study Design and Plan

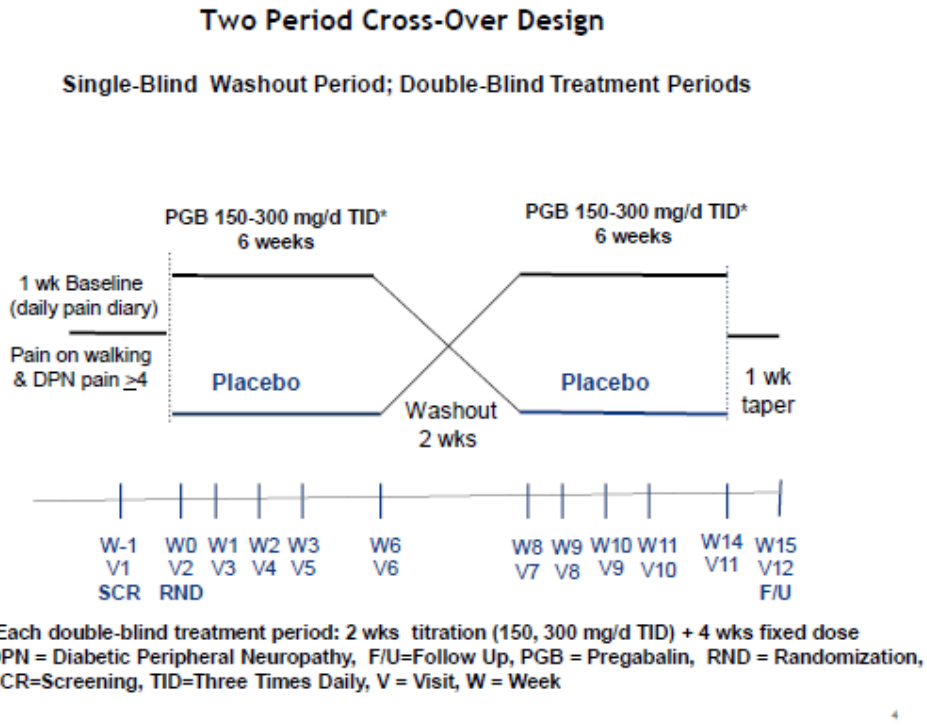

Table 1. Schedule of Activities

Study Phase	Screening	Treatment Period 1					Washout Period	Treatment Period 2					Follow-Up Period
Visit Number	V1[a]	V2[b]	V3	V4[c]	V5	V6/ET[d]		V7[b]	V8	V9[c]	V10	V11/ET[d]	V12[e]
Visit Type	Clinic	Clinic	Phone	Clinic	Clinic	Clinic		Clinic	Phone	Clinic	Clinic	Clinic	Clinic
End of Week	W-1	W0	W1	W2	W3	W6		W8	W9	W10	W11	W14	W15
Study Day (Visit Window)	D-21 to -7	D0	D7±3	D14±3	D21±3	D42±5		D56±5	D63±3	D70±3	D77±3	D98±5	D105±7
End of Period/Week		P1W0	P1W1	P1W2	P1W3	P1W6		P2W0	P2W1	P2W2	P2W3	P2W6	
Informed consent[f]	X												
Demography	X												
Inclusion/ exclusion criteria	X	X											
Medical history	X												
DPN diagnostic worksheet	X												
Physical examination/ abbreviated neurological examination[g]	X					X						X	
12-lead ECG	X												
Clinical laboratory tests	X					X						X	
PHQ-8 (suicidality)	X												
C-SSRS (suicidality)	X	X		X	X	X		X		X	X	X	X
Adverse events	X	X	X	X	X	X		X	X	X	X	X	X
Concomitant medication	X	X	X	X	X	X		X	X	X	X	X	X
Dispense study medication/ dosing diary		X		X	X	X		X		X	X	X	(X)

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Visit Number	V1[a]	V2[b]	V3	V4[c]	V5	V6/ET[d]		V7[b]	V8	V9[c]	V10	V11/ET[d]	V12[e]
Visit Type	Clinic	Clinic	Phone	Clinic	Clinic	Clinic		Clinic	Phone	Clinic	Clinic	Clinic	Clinic
End of Week	W-1	W0	W1	W2	W3	W6		W8	W9	W10	W11	W14	W15
Study Day (Visit Window)	D-21 to -7	D0	D7±3	D14±3	D21±3	D42±5		D56±5	D63±3	D70±3	D77±3	D98±5	D105±7
End of Period/Week		P1W0	P1W1	P1W2	P1W3	P1W6		P2W0	P2W1	P2W2	P2W3	P2W6	
Daily pain/sleep diary (IVRS)[h]	X	X	X	X	X	X		X	X	X	X	X	(X)
Weekly NRS for pain	X												
Pre-walk resting pain (NRS)[i]	X	X											
50 ft walk test and pain (NRS) [i]	X	X			X	X					X	X	
Actigraphy dispense (collect)	X	(X)			X	(X)					X	(X)	
BPI-sf		X				X						X	
QoL-DN		X				X						X	
PGIC						X						X	
PSGA		X				X						X	
HADS		X				X						X	
EQ-5D		X				X						X	
Walk-12		X				X						X	
WPAI-SHP		X											
Healthcare utilization: economic assessment		X											

Table 1. Schedule of Activities

Study Phase	Screening	Treatment Period 1					Washout Period	Treatment Period 2					Follow-Up Period
Visit Number	V1[a]	V2[b]	V3	V4[c]	V5	V6/ET[d]		V7[b]	V8	V9[c]	V10	V11/ET[d]	V12[e]
Visit Type	Clinic	Clinic	Phone	Clinic	Clinic	Clinic		Clinic	Phone	Clinic	Clinic	Clinic	Clinic
End of Week	W-1	W0	W1	W2	W3	W6		W8	W9	W10	W11	W14	W15
Study Day (Visit Window)	D-21 to -7	D0	D7±3	D14±3	D21±3	D42±5		D56±5	D63±3	D70±3	D77±3	D98±5	D105±7
End of Period/Week		P1W0	P1W1	P1W2	P1W3	P1W6		P2W0	P2W1	P2W2	P2W3	P2W6	

BPI-sf = Brief Pain Inventory-Short Form; C-SSRS = Columbia Suicide Severity Rating Scale; D = day, DPN = diabetic peripheral neuropathy; ECG = electrocardiogram; E-Diary = electronic diary; EQ-5D = EuroQoL 5-dimensions questionnaire; ET = early termination; HADS = Hospital Anxiety and Depression Scale; IVRS = interactive voice recognition system; NA = not applicable; NRS = numeric rating scale; P = period; PGIC = Patient Global Impression of Change; PHQ-8 = Patient Health Questionnaire-8; PSGA = Patient Static Global Assessment; QoL-DN = Norfolk Quality of Life Questionnaire for Diabetic Neuropathy; V = visit; W = week; WPAI-SHP = Work Productivity and Activity Impairment Questionnaire-Specific Health Problem; X indicates collection.

a. Visit 1 (Screening) occurred between 21 days and 7 days prior to Visit 2 (randomization) based on the amount of time required for screening procedures, such as washout of prohibited concomitant medication, urine collection for creatinine clearance testing or the risk assessment by a qualified mental health professional. The duration between Visits 1 and 2 was typically approximately 7 days. A 7-day minimum Baseline was required to establish baseline pain level. The maximum 21-day screening period did not include prior completion of the informed consent.
b. Visit 2 was the randomization visit for subjects eligible for enrollment.
c. Visit 4 and Visit 9 constituted the end of the titration phase. The dose was fixed at this visit to the maximum tolerated dose (either 300 or 150 mg/day pregabalin or matching placebo).
d. Visit 6 and Visit 11 were required for subjects who completed or discontinued any portion of the double-blind phase. At Visit 6, 2-week and at Visit 11, 1-week washout/taper medication was dispensed.
e. Visit 12 (follow-up) was for subjects who completed the study or discontinued early after double-blind treatment.
f. Informed consent had to be conducted prior to performing any study procedures, including any medication changes made to participate in the study. Any such medication changes had to be considered for medical appropriateness to protect subject well-being. Informed consent might have been obtained on a separate date in advance of Visit 1 procedures, e.g. informed consent might be obtained 28 days prior to Visit 1 to allow for medication washout.
g. At this visit a physical examination and an abbreviated neurological examination were performed.
h. Electronic IVRS daily diary was an electronic daily diary completed via telephone using IVRS, which includes the daily pain NRS and the daily sleep interference rating scale. The pain and sleep diary were both completed at the end of the day in the evening before bedtime. The diary was completed through the evening before Visit 12 (follow-up). At Screening only, the subject completed the weekly pain NRS.
i. The pre-walk NRS and post-test NRS were part of the standardized walking test and were to be administered together as described in the protocol. The pre-walk test NRS (current pain level in feet and legs) was conducted at Screening and Baseline only, immediately prior to the 50 ft walk test. The post-walk NRS was completed immediately after the 50 ft walk test at all designated visits. The 50 ft walk test consisted of walking 50 ft. (15.2 m) on a flat surface i.e. 25 ft in 1 direction and return).

Number of Subjects (Planned and Analyzed): There were 175-200 subjects planned to achieve 140 completers; 411 subjects were screened, 205 were assigned to treatment, and 203 (101 in pregabalin→placebo treatment sequence and 102 in placebo→pregabalin treatment sequence) were treated and analyzed for safety and efficacy.

Diagnosis and Main Criteria for Inclusion:

Inclusion Criteria:

- Diagnosis of type 1 or 2 diabetes mellitus with current hemoglobin A1c levels of ≤11% and stable on any anti-diabetic medications for at least 30 days prior to randomization.
- Men or women who are at least 18 years old
- Diagnosis of painful DPN for at least 3 months
- Pain on walking, as assessed by a walk test and demonstrate inadequate pain control, as defined: at Visit 1, Screening, a score of ≥4 on the 1-week recall, 0-10-point numerical rating scale (Weekly-Pain NRS), and at Visit 2/Randomization, at least 4 daily pain diaries over the previous 7 days (Baseline) and an average daily DPN pain score of ≥4 on the 0-10 point NRS (daily pain diary).
- Completion of at least 4 daily pain diaries during the screening period.

Exclusion Criteria:

- Inability to walk 50 feet on a flat surface
- Pain on walking due to conditions other than DPN.

Study Treatment: In each double-blind treatment period, those subjects starting treatment with pregabalin received 150 mg/day (50 mg TID) for the first week and 300 mg/day (100 mg TID) for the second week. Once on 300 mg/day, 1 dose reduction was allowed based on tolerability. At the end of the second week, the dose was fixed at the optimized dose for the following 4 weeks. The study medication was administrated orally, TID, with or without food. All eligible subjects entered the study at Visit 1/Screening and completed the 1 week baseline period followed by randomization to either treatment, if eligible. For an overview on dose selection and timing see Table 2 and Table 3. Study medication was supplied as blinded capsules of pregabalin immediate release and matching placebo.

Table 2. Pregabalin and Matching Placebo Dose Escalation Schedule

Pregabalin and Matching Placebo Dose Escalation Schedule for Each Period			
	Day 1-7 (mg/day)	**Day 8[a]-14 (mg/day)**	**Day 15[a]-43 (mg/day)**
Pregabalin dose	150	300	300
Placebo	PBO	PBO	PBO

PBO = placebo; TID = 3 times daily.
a. Dose optimization phase; after Day 14, the subjects remained on a stable maintenance dose.

Table 3. Pregabalin and Matching Placebo Tapering Schedule (TID)

Final Dose	Days 1-3 (mg/day)	Days 4-7 (mg/day)
Pregabalin 300 mg/day	150	0
Pregabalin 150 mg/day	0	0

TID = 3 times daily.

Efficacy Endpoints:

Primary Efficacy Endpoints:

- Reduction in DPN pain, as assessed by the endpoint mean pain score based on the mean of the last 7 daily pain NRS scores from the daily pain diaries while receiving study medication in each treatment period (daily pain diary, 0-10 point NRS)
- Reduction in DPN pain on walking as assessed by the subject's report of DPN pain on walking, using a 0-10 point NRS, that is completed immediately after walking 50 ft (15.2 m) on a flat surface (DPN pain on walking NRS).

Secondary Efficacy Endpoints:

- Responder rate based on a 30% and 50% improvement in mean pain response (from daily pain diary)
- Brief Pain Inventory-short form (BPI-sf)
- Actigraph device worn on hip during waking hours (to measure steps and daytime activity)
- Walk-12
- Norfolk Quality of Life Questionnaire for Diabetic Neuropathy (QOL-DN) modified with 2-week recall
- Patient Global Impression of Change (PGIC), assessed at the end of Period 1 compared to the start of treatment
- Sleep Interference Rating Scale (daily sleep diary)
- Hospital Anxiety and Depression Scale (HADS)
- Euro QoL-5 Dimensions (EQ-5D)

Exploratory analysis: DPN weekly mean pain diary scores from Baseline, 6 weeks in Period 1, 2 weeks washout and 6 weeks in Period 2.

Safety Evaluations: Safety was evaluated by monitoring of adverse events (AEs), physical and neurological examinations, weight assessments, vital signs, clinical laboratory testing

(hematology, blood chemistry, serum pregnancy test, urinalysis), and suicidality using the Columbia-Suicide Severity Rating Scale (C-SSRS) at each clinic visit.

Statistical Methods:

Analysis Sets:

Full Analysis Set (FAS):

Intent-to-Treat (ITT) Population: All subjects who were randomized, treated (ie, received at least 1 dose of study medication) and have at least 1 post-randomization efficacy evaluation. This was the primary analysis set.

'Per-protocol' Analysis Set (PPAS): All randomized subjects who received the study medication and completed the study without any major protocol violations. A completer was defined as any subject who has completed both crossover periods of the study. Major protocol violation criteria were to be defined before database release and before unblinding of the randomization code.

Safety Analysis Set: All subjects who had received at least 1 dose of study medication were to be included in this analysis.

Analysis:

Primary Efficacy:

The primary analysis was conducted using the ITT population. Sensitivity analysis was conducted on the primary endpoint using the PPAS. For all other efficacy analyses (secondary and exploratory analyses) the ITT population was used. All safety analyses were conducted using the safety population.

The co-primary endpoints were the mean pain score at the end of each period (ie. DPN pain), calculated as the mean of the last 7 available pain scores from the daily pain diary, and the 50-ft postwalk pain score (ie, DPN pain on walking). The co-primary endpoint mean weekly DPN pain from the daily diary was analyzed using a linear mixed effects model including baseline pain, sequence, period, center, and treatment as fixed effect factors and subject within sequence and within-subject error as random factors. The treatment difference (pregabalin-placebo) was tested using within-subject variability as the error term. The point estimate for mean treatment difference and corresponding 95% confidence interval (CI) was reported. The analysis was implemented using 'Statistical Analysis System Mixed Procedure. The co-primary endpoint pain on walking at Week 6 was analyzed using a repeated measure (including the Week 3 timepoint) linear mixed effects model including baseline pain at Visit 2, sequence, period, center, time, treatment, and treatment by time interaction as fixed effect factors and subject within sequence and within-subject error as random factors. The study was to be considered positive only if both co-primary endpoints had p-values that were <0.05. The Week 6 comparison (Period 1 and Period 2) was considered primary. A similar test was also applied to secondary efficacy parameters. Descriptive statistics were also reported for the co-primary efficacy endpoints by visit and

treatment group. For DPN pain from the daily diary, an additional sensitivity analysis was conducted using a repeated measure linear mixed model. For pain on walking, another sensitivity analysis was conducted on the average of two pain on walking values at Weeks 3 and 6, and the baseline covariate was the average of screening and baseline pain on walking scores.

Secondary Efficacy:

The analysis of the continuous secondary endpoints was conducted using a last observation carry forward linear mixed model with the same factors as the primary analysis for diary pain except that baseline pain was replaced by the baseline value of the analyzed variable. A Cochran Mantel-Haenszel method and a generalized linear mixed model were used in analysing categorical outcomes.

DPN weekly mean pain diary scores from Baseline, 6 weeks in Period 1, 2 weeks washout and 6 weeks in Period 2 were included in the exploratory analysis. For the purpose of the analysis, it was assumed that subjects were on placebo at Baseline, received the same treatment as in Period 1 during the first week of the washout-period, and were on placebo in the second week of the washout-period. The p-value for the treatment effect was based on a repeated measure mixed effects model including pooled center, time point, treatment, an indicator variable for Week "6" as well as interaction terms as fixed effect factors. The Kenward-Roger method was used to estimate denominator degrees of freedom, and unstructured covariance structure was used to estimate the within subject errors.

Safety:

All AEs were coded with the Medical Dictionary for Regulatory Activities and the incidence was summarized by treatment group, system organ class, and preferred term. The incidence of treatment-emergent adverse events (TEAEs) was displayed by severity and attribution. In addition, the incidence of AEs causing withdrawal and serious adverse events (SAEs) were tabulated. Safety and tolerability data were summarized in tabular format for each dosing group. Any events that occurred in a wash out period were attributed to the preceding treatment. AEs obtained more than 28 days after the last dose of study medication were excluded from all incidence tables.

RESULTS

Subject Disposition and Demography: Table 4 and Table 5 present subject evaluation groups and discontinuations by treatment, respectively. Table 6 presents subject demographic characteristics.

Table 4. Subject Evaluation Groups by Treatment

n (%) of Subjects	Pregabalin	Placebo	All Subjects
Screened			411
Assigned to study treatment			205[a]
Treated	198	186[b]	-
Completed	176 (88.9)	176 (94.6)	-
Discontinued	22 (11.1)	10 (5.4)[b]	-
Analyzed for safety			
AEs	198 (100.0)	186 (100.0)	-
Laboratory data	194[c] (98.0)	186 (100.0)	-

All treated subjects with AE information available were included in the analysis of AEs.
All treated subjects having at least 1 observation for at least 1 laboratory test while on study treatment or during lag time were considered for the analysis of laboratory data.
AE = adverse event; n = number of subjects meeting pre-specified criteria.

a. Two (2) subjects were randomized but discontinued before receiving study treatment.
b. Two (2) subjects in the pregabalin→placebo sequence dropped out in Period 2 and did not take a dose in Period 2, and hence, they were excluded from the placebo group.
c. Four (4) subjects were not evaluable for the laboratory population as they had only a screening assessment or the only post-baseline laboratory exam was >28 days post last dose of study drug.

Table 5. Discontinuations From Study by Treatment

n (%) of Subjects	Pregabalin N=198	Placebo N=186
Discontinuations total	22 (11.1)	10 (5.4)
Related to study drug	7 (3.5)	1 (0.5)
Adverse event	7 (3.5)	1 (0.5)
Not related to study drug	14 (7.1)	9 (4.8)
Death[a]	1 (0.5)	-
Adverse event[a]	2 (1.0)	4 (2.2)
Insufficient clinical response	0 (0.0)	1 (0.5)
Lost to follow-up	2 (1.0)	0 (0.0)
No longer willing to participate in the study	7 (3.5)	3 (1.6)
Other[b]	3 (1.5)	1 (0.5)

AE = adverse event; N = subject population; n = number of subjects meeting pre-defined criteria; SAE = serious adverse event.

a. One (1) subject experienced an SAE and was hospitalized. The subject later died. On the subject summary page, the reason for withdrawal was indicated as AE.
b. One (1) experienced an AE and did not take any medication for approximately 4 weeks. On the subject summary page, the reason for withdrawal was indicated as "Other" ("other illness secondary to preexisting bronchitis").

Table 6. Demographic Characteristics (Safety Population)

Treatment Group	Pregabalin→Placebo			Placebo→ Pregabalin			Overall
	Male	Female	Total	Male	Female	Total	
Number (%) of Subjects	**61 (60.4)**	**40 (39.6)**	**101 (100.0)**	**71 (69.6)**	**31 (30.4)**	**102 (100.0)**	**203 (100.0)**
Age (years)							
Mean (SD)	60.0 (8.4)	57.8 (8.5)	59.1 (8.5)	59.0 (9.3)	59.0 (9.5)	58.4 (9.3)	58.7 (8.9)
Range	40-83	42-76	40-83	34-76	35-73	34-76	34-83
Race n (%)							
White	41 (67.2)	31 (77.5)	72 (71.3)	52 (73.2)	22 (71.2)	74 (72.5)	146 (71.9)
Black	11 (18.0)	4 (10.0)	15 (14.9)	8 (11.3)	4 (12.9)	12 (11.8)	27 (13.3.)
Asian	7 (11.5)	1 (2.5)	8 (7.9)	4 (5.6)	1 (3.2)	5 (4.9)	13 (6.4)
Other	2 (3.3)	4 (10.0)	6 (5.9)	7 (9.9)	4 (12.9)	11 (10.8)	17 (8.4)
Weight (kg)							
Mean (SD)	100.5 (20.4)	92.3 (25.9)	97.2 (23.0)	102.9 (21.9)	93.6 (21.2)	100.1 (22.0)	98.7 (22.5)
Range	59.0-151.8	59.0 (192.3)	59.0 (192.3)	59.9-174.4	54.6-169.4	54.6-174.4	54.6-192.3
Height (cm)							
Mean (SD)	176.6 (8.2)	164.7 (6.0)	171.9 (9.4)	177.4 (8.0)	161.3 (3.8)	172.5 (10.2)	172.2 (9.8)
Range	144.8-195.0	152.4-175.7	144.8-195.0	154.9-200.0	154.0-167.6	154.0-200.0	144.8-200.0
Creatinine clearance							
Mean (SD)	111.3 (38.5)	116.7 (56.0)	113.5 (46.0)	116.1 (40.1)	111.0 (32.5)	114.6 (37.9)	114.0 (42)
Range	65.1-247.9	52.7 (361.0)	52.7 (361.0)	51.3 (276.8)	61.7-200.3	51.3 (276.8)	51.3 (361.0)

n = subject population in specified criteria; SD = standard deviation.

Efficacy Results:

Primary Endpoint Results:

Co-primary Efficacy Endpoint: Reduction in DPN Pain

In the pre-specified primary analysis considering Period 1 and Period 2, a treatment difference of -0.22 points for pregabalin relative to placebo in endpoint mean weekly DPN diary pain score was observed, but did not meet the pre-specified objective (Table 7, p=0.0659). There was evidence that the carry-over and/or the treatment-by-period interaction effect were significant. A non pre-specified analyses using only Period 1 data were performed after the study was unblinded. According to these analyses, treatment with pregabalin resulted in a statistically significantly reduced least squares (LS) mean weekly DPN pain score compared to treatment with placebo in Period 1. A treatment difference of -0.52 points for pregabalin relative to placebo in endpoint mean weekly DPN pain score was observed (p=0.0338).

In the post-hoc exploratory analysis of longitudinal mean weekly DPN pain scores on treatment effects, we observed an LS mean difference (95% CI) of -0.29 (-0.54, -0.04) and a p-value of 0.0242, favoring pregabalin.

Table 7. Statistical Analysis and Summary of Mean Weekly Pain Diary Score (ITT Population) – Co-Primary Endpoint

		Pregabalin N=198	Placebo N=186
Period 1 Week 6	Descriptive statistics		
	n	101	102
	Mean (SD)	4.66 (1.77)	5.29 (1.93)
	Median	4.9	5.2
	Range	1.3-10.0	0.0-10.0
Period 2 Week 6	n	97	84
	Mean (SD)	4.57 (2.22)	4.38 (2.17)
	Median	4.7	4.2
	Range	0.0-9.7	0.0-10.0
	Analysis statistics		
Endpoint Week 6	LS mean (SE)	4.73 (0.14)	4.96 (0.14)
Primary analysis	95% CI LS mean	(4.46, 5.01)	(4.67, 5.24)
Period 1 and 2 (pre-specified)	Pregabalin-placebo		
	LS mean difference (SE)	-0.22 (0.12)	
	95% CI LS mean difference	(-0.46, 0.01)	
	p-Value[a]	0.0659	
Endpoint Week 6	LS mean (SE)	4.80 (0.18)	5.32 (0.18)
Period 1 only (non-pre-specified)	95% CI LS mean	(4.44, 5.15)	(4.97, 5.68)
	Pregabalin-placebo		
	LS mean difference (SE)	-0.52 (0.25)	
	95% CI LS mean difference	(-1.01, -0.04)	
	p-Value[b]	0.0338	

CI = confidence interval; ITT = intent-to-treat; LS mean = least square mean; N = subject population; n = number of subjects meeting pre-defined criteria; SD = standard deviation; SE = standard error.

a. p-Value was based on a linear mixed effects model including baseline pain, sequence, period, pooled center and treatment as fixed effect factors, and subject within sequence and within-subject error as random factors. It considered both Period 1 and Period 2 data.

b. p-Value was based on a linear mixed effects model including baseline pain, pooled center and treatment as fixed effect factors. It considered Period 1 data.

Co-primary Efficacy Endpoint: Reduction in DPN Pain on Walking:

In the pre-specified primary analysis considering Period 1 and Period 2, a treatment difference of -0.13 points for pregabalin relative to placebo in mean DPN pain on walking score at endpoint Week 6 was observed, but did not meet the pre-specified objective (Table 8, p=0.4120).

Table 8. Mixed Model Repeated Measures Analysis of DPN Pain on Walking at Post-Baseline Visits (ITT Population) – Co-Primary Endpoint

		Pregabalin N=198		Placebo N=186
	Analysis statistics			
Endpoint Week 6	LS mean (SE)	4.28 (0.15)		4.41 (0.15)
Primary analysis	95% CI LS mean	(3.98, 4.58)		4.10 (4.71)
Period 1 and 2 (pre-specified)	Pregabalin-placebo			
	LS mean difference (SE)		-0.13 (0.16)	
	95% CI LS mean difference		(-0.44, 0.18)	
	p-Value[a]		0.4120	
Endpoint Week 6	LS mean (SE)	4.03 (0.20)		4.92 (0.19)
Period 1 only (non-pre-specified)	95% CI LS mean	(3.64, 4.43)		(4.54, 5.30)
	Pregabalin-placebo			
	LS mean difference (SE)		-0.89 (0.27)	
	95% CI LS mean difference		(-1.42, -0.36)	
	p-Value[b]		0.0011	

CI = confidence interval; DPN = diabetic peripheral neuropathy; ITT = intent-to-treat; LS mean = least square mean; N = subject population; SE = standard error.

a. p-Value was based on a repeated measure mixed effects model of co-primary endpoint having baseline pain, sequence, period, pooled center, visit, treatment and treatment by visit interaction as fixed effect factors, visit as repeated effect and subject within sequence and within-subject error as random factors. It considered both Period 1 and Period 2 data.

b. p-Value was based on a repeated measure mixed effects model of co-primary endpoint having baseline pain, pooled center, visit, treatment and treatment by visit interaction as fixed effect factors and visit as repeated effect. It considered Period 1 data.

Secondary Endpoint Results:

Pain Responders, ≥30% and ≥50% Pain Reduction:

A subject with at least 30% reduction in endpoint mean DPN pain score from Baseline was defined a 30% pain responder. Responder analysis was also performed using at least 50% pain improvement as the definition of response (Table 9).

Table 9. Mean Pain Reduction From Baseline (ITT - Population)

		Pregabalin N=198	Placebo N=186
	≥30% reduction	n (%)	n (%)
Period 1	Yes	39 (38.6)	25 (24.5)
	No	62 (61.4)	77 (75.5)
Period 2	Yes	45 (46.4)	40 (47.6)
	No	52 (53.6)	44 (52.4)
Overall	Pregabalin-placebo		
	Odds ratio	1.55	
	95% CI for odds ratio	0.94, 2.555	
	p-Value	0.0847	
	≥50% reduction		
Period 1	Yes	24 (23.8)	14 (13.7)
	No	77 (76.2)	88 (86.3)
Period 2	Yes	27 (27.8)	27 (32.1)
	No	70 (72.2)	57 (67.9)
Overall	Pregabalin-placebo		
	Odds ratio	1.38	
	95% CI for odds ratio	0.80, 2.39	
	p-Value	0.2459	

CI = confidence interval; ITT = intent-to-treat; N = subject population; n = number of subjects meeting pre-defined criteria.

Brief Pain Inventory Short Form:

Table 10 presents a descriptive summary by period and the analysis of BPI-sf for pain interference with walking ability.

Table 10. Analysis of Brief Pain Inventory Short Form for Pain Interference With Walking Ability (ITT)

		Pregabalin N=198	Placebo N=186
	Descriptive statistics		
Period 1 Week 6	n	98	102
	Mean (SD)	3.77 (2.45)	4.37 (2.65)
	Median	4.0	4.0
	Range	0.0-10.0	0.0-10.0
Period 2 Week 6	n	91	81
	Mean (SD)	3.38 (2.67)	3.10 (2.71)
	Median	3.0	3.0
	Range	0.0-9.0	0.0-10.0
	Analysis statistics		
Endpoint Week 6	LS mean (SE)	3.75 (0.17)	3.93 (0.18)
Period 1 and 2	95% CI LS mean	(3.40, 4.09)	(3.59-4.28)
	Pregabalin-placebo		
	LS mean difference (SE)	-0.19 (0.17)	
	95% CI LS mean difference	(-0.53, 0.15)	
	p-Value	0.2719	

p-Value was based on a linear mixed effects model including baseline pain, sequence, period, pooled center and treatment as fixed effect factors and subject within sequence and within-subject error as random factors.
CI = confidence interval; ITT = intent-to-treat; LS mean = least square mean; N = subject population; n = number of subjects meeting pre-defined criteria; SD = standard deviation; SE = standard error.

Actigraphy:

Table 11 and Table 12 present the analysis of total activity counts and total activity steps respectively.

Walking Impact Scale (Walk-12):

Table 13 presents the analysis of the Walk-12.

Table 11. Total Activity Counts: Actigraphy Data Collected During Walking Hours at Post-Baseline Visits (ITT)

		Pregabalin N=198	Placebo N=186
	Descriptive statistics		
Period 1 Week 6	N	84	90
	Mean (SD)	64548.68 (70883.24)	72288.36 (58359.11)
	Median	40688.5	51057.3
	Range	(6162.9, 500352.6)	(2489.1, 278961.4)
Period 2 Week 6	n	76	70
	Mean (SD)	65750.45 (51453.28)	57306.65 (45788.36)
	Median	52913.0	46803.5
	Range	(1282.0, 251641.6)	(177.8, 237522.8)
	Analysis statistics		
Endpoint Week 6	LS mean (SE)	64703.14 (4005.00)	64139.75 (4057.89)
Period 1 and 2	95% CI LS mean	(56775.49, 72630.79)	(56107.39, 72172.10)
	Pregabalin-placebo		
	LS mean difference (SE)	563.39 (4098.74)	
	95% CI LS mean difference	(-7549.82, 8676.60)	
	p-Value	0.8909	

p-Value was based on a linear mixed effects model including baseline pain, sequence, period, pooled center and treatment as fixed effect factors and subject within sequence and within-subject error as random factors.
CI = confidence interval; ITT = intent-to-treat; LS mean = least square mean; N = subject population; n = number of subjects meeting pre-defined criteria; SD = standard deviation; SE = standard error.

Table 12. Total Activity Steps: Actigraphy Data Collected During Walking Hours at Post-Baseline Visits (ITT)

		Pregabalin N=198	Placebo N=186
	Descriptive statistics		
Period 1 Week 6	n	82	89
	Mean (SD)	3689.44 (2932.59)	4034.34 (2843.46)
	Median	2856.2	3293.0
	Range	(345.7, 16316.9)	(422.7, 13166.9)
Period 2 Week 6	n	75	69
	Mean (SD)	3830.86 (2632.22)	3394.64 (2644.04)
	Median	3087.4	2887.6
	Range	200.0, 13703.6)	(286.8, 16136.3)
	Analysis statistics		
Endpoint Week 6	LS mean (SE)	3785.65 (201.17)	3788.28 (203.05)
Period 1 and 2	95% CI LS mean	(3387.32, 4183.98)	(3386.21, 4190.34)
	Pregabalin-placebo		
	LS mean difference (SE)	-2.63 (206.37)	
	95% CI LS mean difference	(-411.26, 406.01)	
	p-Value	0.9899	

CI = confidence interval; ITT = intent-to-treat; LS mean = least square mean; N = subject population; n = number of subjects meeting pre-defined criteria; SD = standard deviation; SE = standard error.

Table 13. Analysis of Walking Impact Scale (WALK-12) (ITT)

		Pregabalin N=198	Placebo N=186
	Descriptive statistics		
Period 1 Week 6	n	98	102
	Mean (SD)	36.33 (24.22)	40.91 (24.38)
	Median	33.3	39.6
	Range	(0.0, 97.9)	(0.0, 100.0)
Period 2 Week 6	n	91	81
	Mean (SD)	34.11 (23.31)	31.19 (23.33)
	Median	29.2	27.1
	Range	(0.0, 95.8)	(0.0, 100.0)
	Analysis statistics		
Endpoint Week 6	LS mean (SE)	35.72 (1.44)	37.08 (1.46)
Period 1 and 2	95% CI LS mean	(32.88, 38.55)	(34.20, 39.96)
	Pregabalin-placebo		
	LS mean difference (SE)	-1.37 (1.27)	
	95% CI LS mean difference	(-3.88, 1.15)	
	p-Value	0.2854	

The Walk 12 was a self-administered questionnaire that assesses the impact of the subject's diabetic neuropathy on parameters associated with walking (12 questions) based on a 5-point scale (from not at all to extremely), with higher scores indicating greater impairment.
CI = confidence interval; ITT = intent-to-treat; LS mean = least square mean; N = subject population; n = number of subjects meeting pre-defined criteria; SD = standard deviation; SE = standard error.

Norfolk Quality of Life Questionnaire for Diabetic Neuropathy:

The LS mean difference between the results of pregabalin and placebo treated subjects was -1.46 (95% CI -3.60, 0.68) and did not reach statistical significance (p=0.1805, Table 14). There was no clinically significant difference between pregabalin treatment and placebo treatment with regard to QoL-DN total score or any of its 5 domains (Table 15).

Table 14. Analysis of Norfolk Quality of Life Questionnaire for Diabetic Neuropathy Total Score (ITT)

		Pregabalin N=198	Placebo N=186
	Descriptive statistics		
Period 1 Week 6	n	98	102
	Mean (SD)	30.79 (20.45)	32.45 (19.64)
	Median	25.0	32.0
	Range	(-1.0, 109.0)	(-2.0, 101.0)
Period 2 Week 6	n	91	81
	Mean (SD)	27.53 (19.36)	27.78 (19.30)
	Median	25.0	26.0
	Range	(-1.0, 84.0)	(-2.0, 111.0)
	Analysis statistics		
Total QoL-DN score	LS mean (SE)	29.31 (1.17)	30.77 (1.19)
Endpoint Week 6	95% CI LS mean	(27.00, 31.61)	(28.42, 33.11)
Period 1 and 2	Pregabalin-placebo		
	LS mean difference (SE)	-1.46 (1.09)	
	95% CI LS mean difference	(-3.60, 0.68)	
	p-Value	0.1805	

The QoL-DN was a measure of quality of life. It consisted of a total score and specific domains: symptoms, physical functioning/large fiber, small fiber, activities of daily living and autonomic. The QoL-DN was adapted in this study to measure subject's quality of life over a period of 2 weeks. Higher scores indicated worse quality of life.

CI = confidence interval; ITT = intent-to-treat; LS mean = least square mean; N = subject population; n = number of subjects meeting pre-defined criteria; QoL-DN = Norfolk Quality of Life Questionnaire for Diabetic Neuropathy; SD = standard deviation; SE = standard error.

Table 15. Analysis of Norfolk Quality of Life Questionnaire for Diabetic Neuropathy Domains (ITT - Population)

	Analysis Statistics	Pregabalin N=198	Placebo N=186
Week 6	LS mean (SE)	7.65 (0.32)	7.99 (0.33)
Symptoms score	95% CI LS mean	(7.01, 8.29)	(7.34, 8.64)
	Pregabalin-placebo		
	LS mean difference (SE)	-0.34 (0.33)	
	95% CI LS mean difference	(-0.99, 0.31)	
	p-Value	0.3028	
Week 6	LS mean (SE)	2.36 (0.19)	2.42 (0.20)
Activities of daily living	95% CI LS mean	(1.99, 2.74)	(2.04, 2.81)
	Pregabalin-placebo		
	LS mean difference (SE)	-0.06 (0.18)	
	95% CI LS mean difference	(-0.41, 0.30)	
	p-Value	0.7542	
Week 6	LS mean (SE)	15.51 (0.73)	16.78 (0.75)
Physical functioning/large fiber	95% CI LS mean	(14.06, 16.96)	(15.31, 18.26)
	Pregabalin-placebo		
	LS mean difference (SE)	-1.27 (0.68)	
	95% CI LS mean difference	(-2.62, 0.07)	
	p-Value	0.0634	
Week 6	LS mean (SE)	2.77 (0.17)	2.53 (0.17)
Small fiber	95% CI LS mean	(2.43, 3.11)	(2.18, 2.87)
	Pregabalin-placebo		
	LS mean difference (SE)	0.24 (0.19)	
	95% CI LS mean difference	(-0.13, 0.62)	
	p-Value	0.1985	
Week 6	LS mean (SE)	1.07 (0.10)	1.08 (0.10)
Autonomic	95% CI LS mean	(0.88, 1.27)	0.88 (1.28)
	Pregabalin-placebo		
	LS mean difference (SE)	-0.00 (0.10)	
	95% CI LS mean difference	(-0.21, 0.20)	
	p-Value	0.9686	

The QoL-DN was a measure of quality of life. It consisted of a total score and specific domains: symptoms, physical functioning/large fiber, small fiber, activities of daily living and autonomic. The QoL-DN was adapted in this study to measure subject's quality of life over a period of 2 weeks. Higher scores indicated worse quality of life.
CI = confidence interval; ITT = intent-to-treat; LS mean = least square mean; N = subject population; QoL-DN = Norfolk Quality of Life Questionnaire for Diabetic Neuropathy; SE = standard error.

Patient Global Impression of Change (Period 1):

Table 16 summarizes the results of PGIC assessment after Period 1. In the pre-specified secondary analysis of PGIC at the end of Period 1, the treatment difference was statistically significant (p=0.0020), favouring pregabalin. In addition, the percentage of subjects who reported improvement in their overall status was high at the end of Period 1 (Week 6), with

81.6% of the subjects in the pregabalin treatment group and 58.8% of subjects in the placebo group reporting any improvement (very much, much and minimal improvement). The proportion of subjects reporting any improvement was statistically significantly higher in the pregabalin treatment group (odds ratio [95% CI]: 2.5400 [1.30, 4.95]) compared to placebo.

Table 16. Summary and Analysis of Patient Global Impression of Change Period 1 (ITT - Population) – Secondary Endpoint

	Pregabalin N=198	Placebo N=186
PGIC at Week 6 (Period 1)		
Subject status		
Original score, n (%)	98	102
Very much improved	11 (11.2)	6 (5.9)
Much improved	39 (39.8)	26 (25.5)
Minimally improved	30 (30.6)	28 (27.5)
No change	13 (13.3)	34 (33.3)
Minimally worse	2 (2.0)	6 (5.9)
Much worse	2 (2.0)	1 (1.0)
Very much worse	1 (1.0)	1 (1.0)
Categorized score, n (%)		
Very much improved	50 (51.0)	32 (31.4)
Any improvement	80 (81.6)	60 (58.8)
No change	13 (13.3)	34 (33.3)
Any worsening	5 (5.1)	8 (7.8)
Pregabalin-placebo		
Odd ratio		2.5400
95% CI for odds ratio		(1.30, 4.95)
p-Value		0.0020

Odds ratio was based on the binary response for any improvement while p-value was from the comparison of the original scale of 7 possible outcomes. p-Value was calculated by using Cochran Mantel-Haenszel test.
PGIC values at the end of Period 1 data was compared between treatment groups.
CI = confidence interval; ITT = intent-to-treat; N = subject population; n = number of subjects meeting pre-defined criteria; PGIC = Patient Global Impression of Change.

Sleep Interference Rating Scale (Sleep Diary):

The treatment with pregabalin resulted in statistically significantly more reduction of pain interference compared to treatment with placebo (p=0.0105, Table 17).

Table 17. Analysis of Sleep Interference Rating Scale (ITT)

		Pregabalin N=198	Placebo N=186
	Descriptive statistics		
Period 1 Week 6	n	95	102
	Mean (SD)	3.81 (2.14)	4.20 (2.39)
	Median	3.7	4.0
	Range	(0.0, 10.0)	(0.0, 10.0)
Period 2 Week 6	n	92	81
	Mean (SD)	3.43 (2.31)	3.62 (2.41)
	Median	3.0	3.6
	Range	(0.0, 9.7)	(0.0, 10.0)
	Analysis statistics		
Endpoint Week 6	LS mean (SE)	3.66 (0.12)	4.05 (0.13)
Period 1 and 2	95% CI LS mean	(3.42, 3.91)	(3.80, 4.30)
	Pregabalin-placebo		
	LS mean difference (SE)	-0.38 (0.15)	
	95% CI LS mean difference	(-0.68, -0.09)	
	p-Value	0.0105	

The sleep interference rating scale (a daily sleep diary) consisted of an 11 point numeric rating scale with which the subject rated how painful DPN had interfered with their sleep during the past 24 hours. Zero indicated "does not interfere with sleep" and 10 indicated "completely interferes (unable to sleep due to pain).
CI = confidence interval; DPN = diabetic peripheral neuropathy; ITT = intent-to-treat; LS mean = least square mean; N = subject population; n = number of subjects meeting pre-defined criteria; SD = standard deviation; SE = standard error.

Hospital Anxiety and Depression Score:

At Baseline, subject anxiety and depression scores were in the normal range (0-7). The overall mean (standard deviation [SD]) baseline score of HADS-Anxiety (HADS-A, subscale) was 6.34 (±4.29); the mean (SD) baseline score of HADS-Depression (HADS-D, subscale) was 5.22 (±3.54).

At endpoint Week 6, the mean score of the HADS-A questionnaire was slightly lower in the pregabalin treatment group. The LS mean was 4.65 (95% CI: 4.27, 5.03) for the pregabalin treated subjects and 4.92 (95% CI: 4.54, 5.31) for the placebo treated subjects. The LS mean difference between pregabalin and placebo treated subjects was -0.28 (95% CI -0.63, 0.07), which was not statistically significant (p=0.1178, Table 18).

Similar to the results of HADS-A questionnaire, the mean score of the HADS-D questionnaire was slightly lower in the pregabalin treatment group at endpoint Week 6. The LS mean was 3.73 (95% CI: 3.34, 4.12) for the pregabalin treated subjects and 3.79 (95% CI: 3.57, 4.36) for the placebo treated subjects. The LS mean difference between pregabalin and placebo treated subjects was -0.24 (95% CI -0.60, 0.13), which was not statistically significant (p=0.1990, Table 19).

Table 18. Analysis of Hospital Anxiety and Depression Scale-Anxiety (ITT)

		Pregabalin N=198	Placebo N=186
	Descriptive statistics		
Period 1 Week 6	n	98	102
	Mean (SD)	4.72 (3.68)	5.21 (3.71)
	Median	4.0	5.0
	Range	(0.0, 18.0)	(0.0, 14.0)
Period 2 Week 6	n	91	81
	Mean (SD)	4.59 (3.30)	4.37 (3.77)
	Median	4.0	3.0
	Range	(0.0, 14.0)	(0.0, 18.0)
	Analysis statistics		
Endpoint Week 6	LS mean (SE)	4.65 (0.19)	4.92 (0.20)
Period 1 and 2	95% CI LS mean	4.27 (5.03)	(4.54, 5.31)
	Pregabalin-placebo		
	LS mean difference (SE)	-0.28 (0.18)	
	95% CI LS mean difference	(-0.63, 0.07)	
	p-Value	0.1178	

CI = confidence interval; ITT = intent-to-treat; LS mean = least square mean; N = subject population; n = number of subjects meeting pre-defined criteria; SD = standard deviation; SE = standard error.

Table 19. Analysis of Hospital Anxiety and Depression Scale-Depression (ITT)

		Pregabalin N=198	Placebo N=186
	Descriptive statistics		
Period 1 Week 6	n	98	102
	Mean (SD)	3.98 (3.22)	4.31 (3.65)
	Median	3.0	3.0
	Range	(0.0, 16.0)	(0.0, 15.0)
Period 2 Week 6	n	91	81
	Mean (SD)	3.87 (3.19)	3.60 (3.42)
	Median	3.0	3.0
	Range	(0.0, 11.0)	(0.0, 21.0)
	Analysis statistics		
Endpoint Week 6	LS mean (SE)	3.73 (0.20)	3.97 (0.20)
Period 1 and 2	95% CI LS mean	(3.34, 4.12)	(3.57, 4.36)
	Pregabalin-placebo		
	LS mean difference (SE)	-0.24 (0.18)	
	95% CI LS mean difference	(-0.60, 0.13)	
	p-Value	0.1990	

CI = confidence interval; ITT = intent-to-treat; LS mean = least square mean; N = subject population; n = number of subjects meeting pre-defined criteria; SD = standard deviation; SE = standard error.

European Quality of Life Questionnaire in 5 Dimensions:

The overall mean (SD) baseline results of the EQ-5D were 0.55(±0.26) for both index scores applied. At endpoint Week 6, the results of EQ-5D were in the same range for the pregabalin treatment group and the placebo treatment group (Table 20).

Table 20. Analysis of European Quality of Life Questionnaire in 5 Dimensions

		Pregabalin N=198	Placebo N=186
	Analysis statistics		
Endpoint Week 6	LS mean (SE)	0.649 (0.015)	0.643 (0.015)
Period 1 and 2	95% CI LS mean	(0.620, 0.678)	(0.614, 0.672)
Index score Dolan 1997	Pregabalin-placebo		
	LS mean difference (SE)	0.006 (0.02)	
	95% CI LS mean difference	(-0.025, 0.037)	
	p-Value	0.71107	
Endpoint Week 6	LS mean (SE)	0.650 (0.014)	0.641 (0.014)
Period 1 and 2	95% CI LS mean	(0.622, 0.677)	(0.612, 0.669)
Index score Dolan 2001	Pregabalin-placebo		
	LS mean difference (SE)	0.009 (0.02)	
	95% CI LS mean difference	(-0.021, 0.039)	
	p-Value	0.53965	

p-Value was based on a linear mixed effects model including baseline value, sequence, period, pooled center and treatment as fixed effect factors and subject within sequence and within-subject error as random factors.
CI = confidence interval; LS mean = least square mean; N = subject population; SE = standard error.

Safety Results: A summary of TEAEs experienced by ≥2% during either treatment is shown in Table 21. For TEAEs experienced by ≥ 5% of subjects, an odds ratio was calculated to compare the incidences between the treatment groups (Table 22), respectively. Incidence of treatment-related TEAEs experienced by ≥2 subjects is summarized in Table 23.

Table 21. Incidence of Treatment-Emergent Adverse Events (All Causalities) Experienced by ≥2% of Subjects by Preferred Term

Treatment Group	Pregabalin (N=198)	Placebo (N=186)
TEAEs	**n (%)**	**n (%)**
n (%)[a]		
Somnolence	12 (6.1)	4 (2.2)
Dizziness	11 (5.6)	6 (3.2)
Fatigue	11 (5.6)	3 (1.6)
Oedema peripheral	9 (4.5)	2 (1.1)
Back pain	5 (2.5)	1 (0.5)
Dry mouth	5 (2.5)	1 (0.5)
Headache	5 (2.5)	8 (4.3)
Nausea	5 (2.5)	6 (3.2)
Upper respiratory tract infection	5 (2.5)	8 (4.3)
Weight increased	5 (2.5)	1 (0.5)
Vision blurred	4 (2.0)	1 (0.5)
Constipation	3 (1.5)	4 (2.2)
Diarrhoea	2 (1.0)	5 (2.7)
Total preferred term events	219	165

AEs and SAEs were not separated out.
Subjects were counted only once per treatment in each row. Any missing severities had been imputed as severe. Missing baseline severities were imputed as mild.
Included data up to 28 days after last dose of study drug. Listed in descending order by pregabalin.
Any events that occurred in a wash out period wereattributed to the preceding treatment. MedDRA (v16.0) coding dictionary applied.
AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; N = subject population; n = number of subjects meeting pre-defined criteria; SAE = serious adverse event; TEAE = treatment-emergent adverse event; v = version.

a. Number (%) of subjects with treatment-emergent adverse events by preferred term experienced in ≥2% of subjects in either treatment group by MedDRA preferred term

Table 22. Treatment-Emergent Adverse Events Experienced by ≥5% of Subjects by Preferred Term

Preferred Term	Pregabalin N=198 n (%)	Placebo N=186 n (%)	Pregabalin vs Placebo Odds Ratio (95% CI)
Somnolence	12 (6.1)	4 (2.2)	-[a]
Dizziness	11 (5.6)	6 (3.2)	2.305 (0.65, 8.12)
Fatigue	11 (5.6)	3 (1.6)	2.924 (0.69, 12.44)

AEs and SAEs were not separated out.
MedDRA (v16.0) coding dictionary applied. Any events that occurred in a wash out period were attributed to the preceding treatment.
AE = adverse event; CI = confidence interval; MedDRA = Medical Dictionary for Regulatory Activities; N = subject population; n = number of subjects with adverse event for the given treatment group; SAE = serious adverse events; vs. = versus.

a. Odds ratio for somnolence was not calculated as there were no subjects with somnolence in the placebo group during Period 2.

Table 23. Incidence of Treatment-Emergent Adverse Events (Treatment-Related) Experienced by ≥2 Subjects by Preferred Term

Treatment Group	Pregabalin (N=198)	Placebo (N=186)
TEAEs	**n (%)**	**n (%)**
n (%)[a]		
Somnolence	12 (6.1)	4 (2.2)
Fatigue	10 (5.1)	2 (1.1)
Dizziness	10 (5.1)	5 (2.7)
Oedema peripheral	6 (3.0)	1 (0.5)
Dry mouth	5 (2.5)	1 (0.5)
Weight increase	5 (2.5)	1 (0.5)
Nausea	4 (2.0)	5 (2.7)
Vision blurred	4 (2.0)	1 (0.5)
Anxiety	2 (1.0)	1 (0.5)
Constipation	2 (1.0)	3 (1.6)
Insomnia	2 (1.0)	1 (0.5)
Pruritis	2 (1.0)	1 (0.5)
Tremor	2 (1.0)	0 (0.0)
Headache	0 (0.0)	2 (1.1)
Abnormal dreams	0 (0.0)	2 (1.1)
Diarrhoea	0 (0.0)	4 (2.2)
Total preferred term events (related)	89	60

AEs and SAEs were not separated out.
Subjects were counted only once per treatment in each row. Any missing severities had been imputed as severe unless the subject experienced another occurrence of the same event in a given treatment for which severity was recorded. In this case, the reported severity was summarized. Missing baseline severities were imputed as mild. Included data up to 28 days after last dose of study drug. Listed in descending order by pregabalin. Any events that occurred in a wash out period were attributed to the preceding treatment. MedDRA (v16.0) coding dictionary applied.
AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; N = subject population; n = number of subjects meeting pre-defined criteria; SAE = serious adverse event; TEAE = treatment-emergent adverse event; v = version.
a. Number (%) of subjects with related treatment-emergent adverse events by preferred term experienced in ≥2 subjects in either treatment group by MedDRA preferred term.

Serious adverse events (SAEs) occurred for 9 subjects (4.5%) during pregabalin treatment (16 SAEs) and 2 subjects (1.1%) during placebo treatment (2 SAEs). Evaluated per treatment sequence, more subjects (8 [4.0%]) experienced a SAE in the pregabalin→placebo treatment sequence than in the placebo→pregabalin treatment sequence (3 [1.5%]). SAEs were reported in similar frequencies for both treatment sequences (Table 24). The majority of subjects reported only 1 SAE, and none of the events was reported by more than 1 subject. None of the events was associated with treatment.

Table 24. Incidence of Serious Adverse Events by Preferred Term by Treatment Group and Actual Treatment

Preferred Term	Pregabalin→ Placebo		Placebo→Pregabalin	
	Pregabalin	Placebo	Placebo	Pregabalin
Angina unstable			1	
Back pain			1	
Brain injury			1	
Diabetic ketoacidosis			1	
Drug withdrawal convulsions			1	
Hypoglycemia			1	
Muscular weakness			1	
Pulmonary embolism			1	
Cellulitis	1			
Cerebrovascular accident	1			
Diverticulitis	1			
Intervertebral discitis	1			
Myocardial infarction	1			
Radius fracture	1			
Transient ischemic attack	1			
Urosepsis	1			
Urinary tract infection		1		
Venous thrombosis		1		

MedDRA (v16.0) coding dictionary applied.
MedDRA = Medical Dictionary for Regulatory Activities; v = version.

There were 2 deaths occurred in the study, 1 from cerebral apoplexy (preferred term; a cerebrovascular accident) and one from anoxic brain damage. No death was considered related to study medication.

Table 25 and Table 26 present permanent and temporary discontinuations occurred during the study.

Table 25. Discontinuations Due to Treatment-Emergent Adverse Events (All Causalities)

Treatment[a]/ Serial Number	System Organ Class/MedDRA Preferred Term	Start Day[b]/Stop Day	Severity/Serious (Yes/No)	Outcome/ Study Drug Related?
Pregabalin				
1	Nervous system disorder/dizziness	19/20	Moderate No	Resolved Yes
2	Gastrointestinal disorder/abdominal distension	17/29	Moderate No	Resolved Yes
3	Nervous system disorder/headache	111/112	Mild No	Resolved No
4	General disorder and administration site condition/oedema peripheral	29/40	Mild No	Resolved Yes
5	Nervous system disorder/dizziness	1/16	Moderate No	Resolved Yes
6	Infections and Infestations/pneumonia	25/47	Mild No	Resolved No
7	General disorder and administration site condition/fatigue	7/8	Mild No	Resolved Yes
8	Musculoskeletal and connective tissue disorders/back pain	52/[>73]	Moderate No	Still present No
9	Infections and infestations/urosepsis	47/59	Severe Yes	Resolved No
10	Gastrointestinal disorder/dry mouth	2/[>37]	Moderate No	Still present Yes
11	Musculoskeletal and connective tissue disorders/muscular weakness	79/99	Severe Yes	Resolved No
12	Infections and infestations/ Staphyloccoccal infections	36/56	Severe Yes	Resolved No
13	Nervous system disorder/cerebral ischemia	25/34	Severe Yes	Resolved No
Placebo				
14	Gastrointestinal disorder/nausea	15/28	Moderate No	Resolved Yes
15	Gastrointestinal disorder/vomiting	51/64	Moderate No	Resolved Yes
16	Musculoskeletal and connective tissue disorders/osteoarthritis	65/[>86]	Moderate No	Still present No
17	Vascular disorder/deep vein thrombosis	85/155	Severe Yes	Resolved No
18	Infections and infestations/urinary tract infection	96/[>114]	Severe Yes	Still present No

Note: Results summarized in this table were based on the AE page and differ from the results based on the subject summary page (reason for discontinuation).
MedDRA (v16.0) coding dictionary applied.
AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; v = version.
a. Treatment at onset of adverse event.
b. Day relative to start of study treatment. First day of study treatment = Day 1.

Table 26. Temporary Discontinuations or Dose Reductions Due to Treatment-Related Treatment-Emergent Adverse Events

Treatment[a]/ Serial Number	System Organ Class/MedDRA Preferred Term	Start Day/Stop Day[b]	Severity	Outcome	Causality
1	Psychiatric disorders/anxiety	72/74	Moderate	Resolved	Study drug
2	Nervous system disorders/dizziness	70/70	-[c]	Resolved	Study drug
3	General disorder and administration site condition/fatigue	8/17	Moderate	Resolved	Study drug
4	General disorder and administration site condition/gait disturbance	72/74	Severe	Resolved	Study drug
5	Nervous system disorders/lethargie	8/23	Moderate	Resolved	Study drug
6	Nervous system disorders/mental impairment	9/10	Moderate	Resolved	Study drug
7	Gastrointestinal disorder/nausea	2/3	Moderate	Resolved	Study drug
	Nervous system disorders/dizziness	2/3	Moderate	Resolved	Study drug
8	General disorder and administration site condition/oedema peripheral	9/23	Moderate	Resolved	Study drug
9	Nervous system disorders/drowsiness	1/14	Moderate	Resolved	Study drug
10	Nervous system disorders/somnolence	60/98	Moderate	Resolved	Study drug
11	Investigations/weight increased	6/27	Mild	Resolved	Study drug
	Nervous system disorders/dizziness	6/27	Mild	Resolved	Study drug
Placebo					
12	Gastrointestinal disorder/abdominal discomfort	17/23	Mild	Resolved	Study drug
13	Gastrointestinal disorder/aphthous stomatitis	9/28	Mild	Resolved	Study drug
14	Skin and subcutaneous system disorders/rash pruritic	83/96	Moderate	Resolved	Study drug
15	Nervous system disorders/sedation	12/15	Moderate	Resolved	Study drug

MedDRA (v16.0) coding dictionary applied.
MedDRA = Medical Dictionary for Regulatory Activities; v = version.
a. Treatment at onset of adverse event.
b. Day relative to start of study treatment. First day of study treatment = Day 1.
c. Missing entry.

There were no clinically significant laboratory findings apart from the expected anomalies in blood glucose and glycosylated hemoglobin (HbA1c), attributable to diabetes. The median change of HbA1c from Baseline to last observation was 0.0% in the pregabalin treatment group and 0.1% in the placebo treatment group. Median change from Baseline for blood glucose was 6 mg/dL for pregabalin and 7 mg/dL for placebo.

There were no clinically significant physical examination findings at Screening (Visit 1) or at Post-baseline Visits. There were no clinically significant electrocardiogram findings at Screening (Visit 1) for randomized subjects.

Overall, 7 subjects (3.5%) in the pregabalin group and 3 subjects (1.6%) in the placebo group reported a weight gain of ≥7%. A weight gain of ≥10% was reported by 3 subjects during pregabalin treatment and by 2 subjects during placebo treatment. The overall mean weight at Screening was 98.7 kg; the mean weight at Week 6 of Period 2 was 99.6 kg in the pregabalin group and 98.8 kg in the placebo group.

No clinically relevant changes from Baseline were observed in neurological examinations.

Columbia-Suicide Severity Rating Scale:

At Screening, 3 of 102 subjects in the placebo→pregabalin treatment group had a yes-response to 1 of the 12 items of the C-SSRS (Table 27), indicating a potentially increased risk of suicide, however, all these events occurred more than 10 years ago and no mental health risk assessment was performed subsequently. No subjects met any of the criteria of the C-SSRS indicating an elevated suicidal risk at Baseline or during the active treatment phase or during the follow-up period of the study.

Table 27. Descriptive Statistics of C-SSRS (Safety Population) at Screening

		Pregabalin→Placebo N=101	Placebo→ Pregabalin N=102
Screening (lifetime)	Number assessed, n (%)	101 (100)	102 (100)
	Wish to be dead	0.0	1 (1.0)
	Non-specific thoughts	0.0	0.0
	Without intent to act	0.0	0.0
	Some intent to act	0.0	0.0
	Specific plan and intent	0.0	0.0
	Actual attempt	0.0	2 (2.0)
	Non-suicidal self-injurious behavior	0.0	0.0
	Interrupted attempt	0.0	0.0
	Aborted attempt	0.0	0.0
	Preparatory act of behavior	0.0	0.0
	Suicidal behavior present	0.0	0.0
	Completed suicide	0.0	0.0

C-SSRS = Columbia Suicide Severity Rating Scale; N = subject population; n = number of subjects meeting pre-defined criteria.

Mental Health Risk Assessment:

Three (3) subjects with a potentially increased risk were identified at Screening: all 3 subjects were noted with patient health questionnaire-8 total score of ≥15. For these 3 subjects, mental health risk assessments were performed and as a result all subjects were eligible to enter the study. No risk assessments were required and none was performed during the double-blind treatment in Period 1 or Period 2.

CONCLUSION: In adults with DPN pain mean weekly DPN pain diary and mean DPN pain on walking at endpoint Week 6, considering both treatment periods, did not meet the pre-specified primary efficacy objectives (no significant difference between subjects treated with pregabalin and subjects treated with placebo in the ITT population). There were treatment differences in favor of pregabalin on weekly DPN diary pain score and DPN pain on walking at Week 6 although not statistically significant. Regarding the secondary parameters, the PGIC assessed for Period 1 (compared to Baseline) and the results of the sleep interference rating scale assessed over both periods were statistically significantly in favor of pregabalin. The other secondary endpoints did not meet the prespecified objectives.

The study medication was well-tolerated, and most AEs were of mild or moderate intensity. There were no SAEs considered by the Investigator to be related to pregabalin treatment. During both treatment periods of the study, AEs were consistent with known AEs of pregabalin, with somnolence, fatigue, and dizziness being among the most frequent.