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

PROTOCOL NO.: A0081194

PROTOCOL TITLE:

A Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Multi-Center Trial of Pregabalin Controlled Release Formulation as Adjunctive Therapy in Adults With Partial Onset Seizures

Study Centers:

A total of 72 centers took part in the study and enrolled subjects: 18 centers in the United States (US); 7 centers in India; 6 centers each in Germany and Russian Federation; 5 centers each in Bulgaria and Mexico; 4 centers each in Hungary and Poland; 3 centers in Czech Republic; 2 centers each in Hong Kong, Malaysia, Romania, Singapore and Thailand; and 1 center each in Argentina, Bosnia and Herzegovina, Puerto Rico and Serbia.

Study Initiation and Final Completion Dates:

17 February 2011 and 01 August 2012

Phase of Development:

Phase 3

Study Objectives:

Primary Objective: To evaluate the efficacy of 2 different dosages of pregabalin controlled release (CR) administered once daily as compared to placebo as adjunctive treatment in reducing the frequency of seizures in partial onset epilepsy, utilizing the endpoint of log-transformed 28-day partial seizure rate, in adult subjects with partial onset seizures.

Secondary Objectives:

- To characterize the efficacy of pregabalin CR versus placebo on the frequency of partial seizures as determined by responder rate and percentage change from Baseline on 28-day partial seizure rates;
- To characterize the effects of pregabalin CR versus placebo on measures of anxiety, sleep disturbance, and treatment satisfaction;
- To assess the safety and tolerability of pregabalin CR in adult subjects with partial onset seizures.

METHODS

Study Design:

This study was a randomized, double-blind, 3 arm parallel-group, placebo-controlled, multicenter, multinational study in subjects requiring additional treatment for partial onset seizures.

The duration of this study was approximately 23 weeks, with the following 4 standard phases:

- Phase 1 - An 8-week baseline observation phase;
- Phase 2 - A 2-week dose escalation phase;
- Phase 3 - A 12-week double-blind maintenance phase (fixed-dose); and
- Phase 4 - A 1-week taper phase.

Eligible subjects were randomly assigned to 1 of the 3 treatment groups to receive either pregabalin CR 165 mg, pregabalin CR 330 mg or placebo in a 1:1:1 ratio. Details of study visits and procedures are provided in Table 1.

Table 1. Schedule of Activities

Study Activity	Screening/Baseline Visits (8 Weeks)		Dose Escalation Phase (2 Weeks)	Double-Blind Maintenance Phase (12 Weeks)			End of Treatment (EoT) Taper (1 Week)		EoT No Taper (nt)[a,b]
	Visit 1 Week-8	Visit 2 Week-4	Visit 3 (Week 0)	Visit 4 (Week 2)	Visit 5 (Week 6)	Visit 6 (Week 10)	EoT Start Taper (st)	EoT End Taper (et)	
							Visit 7 st[c] (Week 14 st)	Visit 8 (Week 15 et)	Visit 7 nt[c] (Week 14 nt)
	Day -56 ±3	Day-28 ±3	Day 1 0	Day 15 ±3	Day 43 ±3	Day 71 ±3	Day 99 ±3	Day 106 ±3	Day 99 ±3
Informed consent[d]	X								
Medical history	X								
Physical examination	X		X					X	X
Neurological examination[e]	X		X					X	X
Review inclusion/exclusion criteria	X	X	X						
EEG (if none in past 2 years)	X								
CT/MRI (if none in past 2 years)	X								
Diagnostic & seizure classification forms (including EEG & brain CT/MRI results)[f]	X	X	X						
Weight[g]/vital signs (BP and pulse)	X		X					X	X
Laboratory									
Hematology	X							X	X
Blood chemistry	X							X	X
Urinalysis[h]	X							X	X
Pregnancy test[i]	X		X					X	X
12 lead ECG	X							X	X
Pharmacokinetic sample				X	X	X			
Diaries									
Dispense and review seizure diary[j]	X	X	X	X	X	X	X		
Review and collect seizure diary from prior visit[k]		X	X	X	X	X	X	X	X
Dispense and review dosing diary[l]			X	X	X	X	X		
Review and collect dosing diary from prior visit[m]				X	X	X	X	X	X
Assessments									

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	Visit 1 Week-8	Visit 2 Week-4	Visit 3 (Week 0)	Visit 4 (Week 2)	Visit 5 (Week 6)	Visit 6 (Week 10)	EoT Start Taper (st)	EoT End Taper (et)	
							Visit 7 st[c] (Week 14 st)	Visit 8 (Week 15 et)	Visit 7 nt[c] (Week 14 nt)
	Day -56 ±3	Day-28 ±3	Day 1 0	Day 15 ±3	Day 43 ±3	Day 71 ±3	Day 99 ±3	Day 106 ±3	Day 99 ±3
HADS[n]			X				X[n]		X[n]
MOS-SS[n]			X				X[n]		X[n]
BSW[n]							X[n]		X[n]
S-STS[o]	X	X	X	X	X	X	X	X	X
PHQ-8	X								
Review and record concomitant medications (including lifetime AEDs)	X	X	X	X	X	X	X	X	X
Review and record concomitant non-drug treatments and procedures	X	X	X	X	X	X	X	X	X
Randomization			X						
Dispense study medication			X	X	X	X	X		
Review study medication dosing			X	X	X	X	X		
Document reason for end of treatment without a taper[a]									X
Adverse event recording	←							→	

AED = anti-epileptic drug; BP = blood pressure; BSW = benefit, satisfaction, willingness to continue measure; C-SSRS = Columbia Suicide Severity Rating Scale; CT = computed tomography; ECG = electrocardiogram; EEG = electroencephalogram; EoT = end of treatment; ET = early termination; et = end taper; HADS = Hospital Anxiety and Depression Scale; IEC = Independent Ethics committee; IRB = Institutional Review Board; MOS-SS = Medical Outcome Study-Sleep Scale; MRI = magnetic resonance imaging; nt = no taper; PHQ = Patient Health Questionnaire; st = start taper; and S-STS = Sheehan Suicidality Tracking Scale.

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	Visit 1 Week-8	Visit 2 Week-4	Visit 3 (Week 0)	Visit 4 (Week 2)	Visit 5 (Week 6)	Visit 6 (Week 10)	EoT Start Taper (st)	EoT End Taper (et)	
							Visit 7 st[c] (Week 14 st)	Visit 8 (Week 15 et)	Visit 7 nt[c] (Week 14 nt)
	Day -56 ±3	Day-28 ±3	Day 1 0	Day 15 ±3	Day 43 ±3	Day 71 ±3	Day 99 ±3	Day 106 ±3	Day 99 ±3

a. After finishing the study, subjects could be switched directly to pregabalin without taper. All other circumstances required prior discussion with the study team. If the subject completed the study without a taper, the rationale was documented.
b. If subject left the study prior to the completion of double-blind period (ie, early termination) and the taper was not deemed necessary, then ET/nt was the last visit for the study.
c. The last visit for purposes of calculating the end of the per-protocol period for the endpoints.
d. Must have been completed prior to any other study procedures.
e. A brief neurological examination was done at Visit 3.
f. EEG and/or CT/MRI not done within the past 2 years, completed and sent the Epilepsy Diagnostic Verification Form, and Seizure Classification Verification Form, and EEG and CT/MRI records. Diagnosis for inclusion must have been verified before Visit 3.
g. Included weight, height (baseline only), blood pressure, and pulse.
h. Urine dip stick at the center. If abnormal, then a sample was sent to the central laboratory for evaluation.
i. For female subjects of child-bearing potential only. Pregnancy tests were repeated as per request of IRB/IECs or if required by local regulations. Positive pregnancy tests were confirmed by serum pregnancy tests.
j. Seizure diary: Seizure phenomenology was reviewed with the subject. The seizure key was filled out with any updates since the last visit. Subject and caregiver were instructed on how to fill out the diary each day between this visit and the next visit.
k. Reviewed the completed seizure diary. Looked for and discussed findings with the subject and caregiver. Re-educated if necessary. Updated the next seizure key for changing or new seizure subtypes. Findings may have included missing dates, same date twice, new seizure subtype, score marks in the wrong subcategory, and notes in the margin, among others.
l. Dosing diary: Reviewed how to take the medication with the subject and caregiver, if applicable. Ensured that the subject or caregiver understood how to properly take the medication, what to do if the 1 hour window after the evening meal was missed, and if subsequent options were also missed. Instructed the subject, and caregiver as applicable, on how to fill in the diary each day. The medication must have been taken intact. It should not have been bitten, chewed, cut, or otherwise altered prior to swallowing.
m. Reviewed the completed dosing diary: Looked for and discussed findings with the subject and caregiver, as applicable. Re-educated around dosing and filling the diary as necessary.
n. HADS, MOS-SS, and BSW upon completion of the study. For subjects who completed the study as scheduled or discontinued early, these assessments were only completed at Visit 7. If the subject tapered, they were not done at the final visit, which was Visit 8.
o. Assessment of suicidal ideation and behavior: the C-SSRS replaced the S-STS for subjects screened following approval, initiation, and availability of the materials. Subjects continued to be assessed with whichever scale was given to them at their Screening Visit 1.

Number of Subjects (Planned and Analyzed):

Approximately 264 subjects were planned for the study (88 subjects per treatment group). A total of 400 subjects were screened for inclusion, of which 325 subjects were assigned to treatment (pregabalin CR 165 mg: 101 subjects; pregabalin CR 330 mg: 114 subjects; placebo: 110 subjects). Two (2) subjects were randomized but not treated (1 subject in each pregabalin CR treatment group). A total of 323 subjects received at least 1 dose of double-blind treatment (pregabalin CR 165 mg: 100 subjects; pregabalin CR 330 mg: 113 subjects; placebo: 110 subjects) and were analyzed. The 323 subjects included per country were as follows: Argentina, 1; Puerto Rico, 2; Hong Kong, 3; Bosnia and Herzegovina, 5; Singapore, 5; Malaysia, 9; Romania, 9; Czech Republic, 10; Serbia, 16; Poland, 17; Hungary, 18; Germany, 21; India, 24; Mexico, 25; the US, 31; Bulgaria, 41; Russian Federation, 42; Thailand, 44.

Diagnosis and Main Criteria for Inclusion:

Male and female subjects aged ≥18 years with a diagnosis of epilepsy with partial onset seizures (seizures permitted to be simple or complex, with or without evolution into a bilateral, convulsive seizure). Subjects had to be taking 1 to 3 current anti-epileptic drugs (AEDs) at stable dosages, and had to have taken at least 2 prior (or ongoing) AEDs.

Main Exclusion Criteria: Subjects with primary generalized seizure (for example, absence, myoclonic seizures or Lennox-Gastaut syndrome), or status epilepticus within 1 year prior to screening were excluded from the study.

Study Treatment:

Subjects were randomized to receive either pregabalin CR 165 mg, pregabalin CR 330 mg or placebo. Study treatment was provided as blinded tablets of pregabalin CR (82.5 mg, 165 mg and 330 mg strengths) and matching placebo.

Throughout the study, 1 tablet was administered orally, and taken within 1 hour after the evening meal for 15 weeks (Phase 2 plus Phase 3 plus Phase 4). Subjects were instructed to take the medication intact and not bitten, chewed, cut, or otherwise altered prior to swallowing. Subjects were specifically instructed not to take the tablet at the start of the evening meal. If the subject did not take study medication within 1 hour of completion of the evening meal, the tablet was to be administered prior to bedtime with food. If the dose was not taken after the evening meal or at bedtime, the dose was to be administered the following morning with food. Doses not taken by this time were omitted. In each circumstance, the next dose was the regularly scheduled dose in the evening for that day.

For Phase 2 (dose escalation - Day 1 to Day 14), all subjects received medication doses as described in Table 2.

Table 2. Study Medication Dose Escalation Phase Schedule (Day 1 to Day 14)

Dose Group	Day 1 (mg QD)	Day 2 (mg QD)	Day 3 (mg QD)	Day 4 to 14 (mg QD)	Day 15 (mg QD)
Pregabalin CR 165 mg	82.5	82.5	82.5	165	165
Pregabalin CR 330 mg	82.5	82.5	82.5	165	330
Placebo	Placebo	Placebo	Placebo	Placebo	Placebo

CR = controlled release; QD = once daily.

Beginning at Visit 4 (Day 15), subjects received the full randomized dose for Phase 3 (12-week double-blind maintenance) and continued to take their medication each day immediately (within 1 hour) after finishing the evening meal for 12 weeks. This was a fixed dose study; the dose was not changed during the study. Subjects who were unable to tolerate study medication during the escalation or maintenance phase could have been discontinued. At Visit 7 (Day 99), all subjects tapered study medication over 1 week as indicated in Table 3.

Table 3. Study Medication Taper Schedule

Dose Group	Taper Day						
	Day 1 (mg QD)	Day 2 (mg QD)	Day 3 (mg QD)	Day 4 (mg QD)	Day 5 (mg QD)	Day 6 (mg QD)	Day 7 (mg QD)
Pregabalin CR 165 mg	165	165	165	165	165	165	165
Pregabalin CR 330 mg	165	165	165	165	165	165	165
Placebo	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo

CR = controlled release; QD = once daily.

Efficacy and Safety Endpoints:

Primary Endpoints:

- The log-transformed (log_e) 28-day seizure rate for all partial onset seizures collected during the double-blind maintenance treatment phase.

Secondary Efficacy Endpoints:

- Responder rate (proportion of subjects who have a ≥50% reduction in partial seizure rate from Baseline collected during the double-blind maintenance treatment phase compared to the 8-week baseline (screening) (seizure observation) phase;
- The percentage change in 28-day partial seizure rates summarized by treatment group during the double-blind maintenance treatment phase;
- Frequency of secondary generalized tonic-clonic seizures (SGTC) during the double-blind maintenance treatment phase;
- Log-transformed 28-day SGTC rate for all SGTCs collected during the double-blind maintenance treatment phase;

- SGTC responder rate during the double-blind maintenance treatment phase;
- Log-transformed (log_e) 28-day seizure rate for all partial onset seizures collected during the double-blind maintenance treatment phase only;
- Changes from Baseline in the anxiety and depression scores of the Hospital Anxiety and Depression Scale (HADS) scores;
- Change from Baseline in Medical Outcomes Study-Sleep Scale (MOS-SS) domain scores;
- Global scores on the subject-rated Benefit, Satisfaction, and Willingness to continue measure (BSW).

Safety Endpoints:

- Medical history, physical exams, neurological exams, suicidal ideation and behavior assessments (Sheehan Suicidality Tracking Scale [STS] / Columbia Suicide Severity Rating Scale [C-SSRS]). Patient Health Questionnaire (PHQ-8), vital signs, electrocardiogram (ECG), clinical laboratory assessments, adverse events (AEs).

Safety Evaluations:

Laboratory assessments, physical and neurological examinations, vital signs, ECGs, PHQ-8, STS, C-SSRS, AEs, and serious adverse events (SAEs).

Statistical Methods:

The intent-to-treat (ITT) population consisted of all randomized subjects who received at least 1 dose of double-blind treatment, and had a baseline and at least 1 follow-up double-blind treatment phase assessment visit. The ITT population was the primary population.

The per-protocol (PP) population was a subset of the ITT population, which excluded all major study deviators that would impact efficacy.

All subjects with at least 1 dose of study medication were included in the safety population for analyses.

Descriptive statistics (number, mean, standard deviations, median, and the range of minimum to maximum values) were provided for the primary and secondary efficacy variables.

The 28-day seizure rate for the primary endpoint was calculated for each subject using the following algorithm:

$$\text{28-day seizure rate} = \frac{\text{Number of seizures during double-blind treatment phase}}{\text{[Number of days during double-blind treatment phase} - \text{Number of missing diary days during double-blind treatment phase]}} \times 28$$

A log-transformation was applied to the 28-day seizure rate for each subject (ie, $\log_e$ [28-day seizure rate +1]).

The primary analysis of the primary endpoint utilized a linear model with the following fixed terms:

- $\log_e$ (28-day baseline seizure rate +1) as a continuous covariate;
- Geographic area of the study centers (US, European Union [EU], Asia, or rest of world);
- Treatment group (placebo, pregabalin CR 165 mg, pregabalin CR 330 mg).

There were 2 pair-wise comparisons of interest: 1) pregabalin CR 330 mg-placebo, and 2) pregabalin CR 165 mg- placebo. The difference in the least squares (LS) mean and their standard errors (SE) for these 2 pair-wise comparisons were used for constructing test statistics and 2-sided 95% confidence intervals (CI).

A sequential step-wise testing procedure was used to control multiplicity of testing such that the experiment-wise type 1 error rate would not exceed the 5% level of significance. The first step tested the null hypothesis of equal treatment effect of pregabalin CR 330 mg treatment group versus the placebo treatment group with 2-sided test, α=0.05.

Responder Rate: The responder rate was defined by the percentage of subjects who responded to the double-blinded treatment. Subjects who had a ≥50% reduction in the 28-day partial seizure rate from Baseline during the double-blind treatment phase (Visit 3 to Visit 7) were defined as responders, otherwise they defaulted to non-responders. This secondary endpoint was analyzed using a 2-sided Cochran-Mantel-Haenszel test stratified by geographical region in which the study center resided (US, EU, Asia, or rest of world). No adjustments for multiplicity were taken, and nominal p-values from 2-sided test were reported.

The Percentage Change in 28-Day Partial Seizure Rates: The percentage change from Baseline in 28-day partial seizure rate was defined as:

$$\text{\% Change} = \frac{(\text{28-day seizure rate}_t - \text{28-day seizure rate}_b)}{\text{seizure rate}_b} \times 100$$

'$_t$' refers to the double-blind treatment phase (Visit 3 to Visit 7), and
'$_b$' refers to the 8-week baseline period.

This secondary endpoint was summarized by treatment group using the LS means with 2-sided 95% CI based on the primary analysis model.

Frequency of SGTC: The SGTC seizure frequency during the double-blind treatment phase (Visit 3 to Visit 7) was analyzed using a generalized linear model accounting for treatment and geographical region as fixed effects and baseline seizure frequency as a covariate. The testing of treatment group differences of each pregabalin dose minus placebo was estimated using the LS means and appropriate SE of the differences from the model.

Log-Transformed 28-day SGTC Rate for All SGTCs Collected During the Double-Blind Maintenance Phase: This was analyzed for the maintenance phase only (Visit 4 to Visit 7) utilizing the linear model with the following fixed terms:

- Log_e (28-day baseline SGTC rate + 1) as a continuous covariate;
- Geographic area of the study centers (US, EU, Asia, or rest of world);
- Treatment group (placebo, pregabalin CR 165 mg, pregabalin CR 330 mg).

The 28-day SGTC double-blind maintenance seizure rate was calculated for each using the following algorithm:

$$\text{28-day seizure rate} = \frac{\text{Number of SGTC seizures in double-blind maintenance phase}}{\text{(Number of days in double-blind maintenance phase - Number of missing diary days in double-blind treatment phase)}} \times 28$$

SGTC Responder Rate: The SGTC responders were subjects who showed a reduction in the proportion of SGTC/all partial seizures (SGTC 28-day rate divided by the all partial 28-day rate, calculated for both baseline and during the double-blind treatment phase [Visit 3 to Visit 7]).

$$\text{Change in SGTC} = \frac{\text{SGTC rate}_t}{\text{All partial seizure rate}_t} - \frac{\text{SGTC rate}_b}{\text{All partial seizure rate}_b}$$

't' refers to the double-blind treatment phase (Visit 3 to Visit 7), and
'b' refers to the 8-week baseline period.

The SGTC responder rate was analyzed using a 2-sided Cochran-Mantel-Haenszel test stratified by geographic region in which the study center resided (US, EU, Asia, or rest of world), with percentage of responders summarized by treatment group.

Log-Transformed (log_e) 28-Day Seizure Rate for All Partial Onset Seizures Collected During the Double-Blind Maintenance Phase: This was calculated utilizing the same model as the primary endpoint, however during the double-blind maintenance phase only (Visit 4 to Visit 7).

Changes From Baseline in the HADS Scores: The HADS subscales of anxiety (HADS-A) and depression (HADS-D) was analyzed separately using the linear model with fixed terms similar to that described above for the primary analysis. The response variable was the change from Baseline to Visit 7.

Change From Baseline in MOS-SS Scores: Each of the MOS-SS subscale scores were descriptively compared for randomized treatment groups at Baseline, Visit 7, and/or Termination Visit. Change from Baseline to Visit 7 was analyzed using a linear model similar to that described above for the primary analysis, with the exception of the Optimal Sleep subscale. For the Optimal Sleep subscale a logistic regression model was used for fixed effects for treatment, geographic region, and average hours per night of sleep at Baseline as a continuous covariate.

Global Scores on the BSW: The 3 component questions of the BSW were analyzed separately at the End of the Double-Blind Maintenance Phase using the ITT population using a proportional odds model with fixed effects for treatment and geographic region.

Safety: Baseline assessments were done at Day 1 (Visit 3). If Visit 3 data were missing, the last available observation prior to the start of study treatment was considered as a baseline.

RESULTS

Subject Disposition and Demography:

A total of 400 subjects were screened for inclusion in this study, of which 325 subjects were assigned to a treatment group and 323 subjects received at least 1 dose of double-blind treatment. Two (2) subjects were randomized but not treated (1 subject in each pregabalin treatment group). Subject disposition is summarized in Table 4.

A total of 287 subjects completed the study and 36 treated subjects were discontinued from the study (Table 5). The primary reasons of subject discontinuations in all treatment groups were due to AEs and subject no longer willing to participate in the study.

Table 4. Subject Evaluation Groups

Number of Subjects	Pregabalin 165 mg n (%)	Pregabalin 330 mg n (%)	Placebo n (%)
Screened = 400			
Assigned to study treatment	101 (100.0)	114 (100.0)	110 (100.0)
Treated	100 (99.0)	113 (99.1)	110 (100.0)
Completed	91 (90.1)	98 (86.0)	98 (89.1)
Discontinued	9 (8.9)	15 (13.2)	12 (10.9)
Analyzed for efficacy	100 (99.0)	112 (98.2)	109 (99.1)
Intent-to-treat	100 (99.0)	112 (98.2)	109 (99.1)
Per-protocol	81 (80.2)	88 (77.2)	90 (81.8)
Analyzed for safety	100 (99.0)	113 (99.1)	110 (100.0)
Safety population	100 (99.0)	113 (99.1)	110 (100.0)
Adverse events	100 (99.0)	113 (99.1)	110 (100.0)
Laboratory data	99 (98.0)	111 (97.4)	108 (98.2)

Discontinuations attributed to the last study treatment received.
Subjects could have been excluded from a population for multiple reasons.
n = number of subjects in specified criteria.

Table 5. Discontinuations From Study

Number (%) of Subjects	Pregabalin 165 mg (N=100) n (%)	Pregabalin 330 mg (N=113) n (%)	Placebo (N=110) n (%)	Overall (N=323) n (%)
Discontinuations	9 (9.0)	15 (13.3)	12 (10.9)	36 (11.1)
Subject died	0	0	0	0
Did not meet entrance criteria	0	2 (1.8)	0	2 (0.6)
Insufficient clinical response	0	0	1 (0.9)	1 (0.3)
Lost to follow-up	1 (1.0)	0	2 (1.8)	3 (0.9)
No longer willing to participate in study	3 (3.0)	3 (2.7)	2 (1.8)	8 (2.5)
Other	2 (2.0)	1 (0.9)	3 (2.7)	6 (1.9)
Protocol violation	0	1 (0.9)	1 (0.9)	2 (0.6)
Adverse event	3 (3.0)	8 (7.1)	3 (2.7)	14 (4.3)
Related to study drug	3 (3.0)	8 (7.1)	3 (2.7)	14 (4.3)
Adverse event, not serious	3 (3.0)	6 (5.3)	3 (2.7)	12 (3.7)
Adverse event, serious non-fatal	0	2 (1.8)	0	2 (0.6)
Adverse event, serious fatal	0	0	0	0
Not related to study drug	0	0	0	0
Adverse event, not serious	0	0	0	0
Adverse event, serious non-fatal	0	0	0	0
Adverse event, serious fatal	0	0	0	0

N = total number of subjects; n = number of subjects in specified criteria.

Among treated subjects, approximately 52% were female (169 of 323 subjects). Demographic characteristics are summarized in Table 6.

Table 6. Demographic Characteristics (Safety Analysis Set)

Demographic Characteristics	Pregabalin 165 mg (N=100)	Pregabalin 330 mg (N=113)	Placebo (N=110)
Age (years)			
18 to 44, n (%)	72 (72.0)	74 (65.5)	76 (69.1)
45 to 64, n (%)	26 (26.0)	35 (31.0)	30 (27.3)
≥65, n (%)	2 (2.0)	4 (3.5)	4 (3.6)
Mean (SD)	37.9 (13.1)	39.6 (13.1)	38.7 (13.2)
Range	18 to 70	18 to 75	18 to 72
Sex, n			
Male	47	58	49
Female	53	55	61

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

Efficacy Results:

The percent reduction for all partial seizures except those without a motor component for subjects in the pregabalin CR 300 mg treatment group was not statistically significantly different from the percent reduction in the placebo group (p=0.0907) as summarized in Table 7. The percent reduction for all partial seizures except those without a motor component for subjects in the pregabalin CR 165 mg treatment group was similar to placebo (p=0.9076).

Table 7. Summary of ANCOVA Log Transformed 28-Day Seizure Rate (All Partial Except Those Without Motor Component) During the Double-Blind Treatment Phase – Overall (ITT Population)

	N	Baseline Value Mean (SD)	N	Overall Observed Value Mean (SD)	Versus Placebo (%), ANCOVA LS Mean Diff	95% CI	p-Value
Pregabalin 165 mg	100	2.24 (0.757)	98	1.84 (1.003)	-0.99	-16.28, 17.11	0.9076
Pregabalin 330 mg	112	2.33 (0.873)	111	1.80 (1.030)	-13.05	-26.07, 2.25	0.0907
Placebo	109	2.32 (0.910)	109	1.93 (1.132)	-	-	-

Percent reduction in seizures was calculated as follows: 100% * (exp [x] – 1) = %, where x is the log value.
Overall refers to all treatment days during the double-blind treatment phase.
Estimates and p-values were from the ANCOVA model including fixed effects for baseline value, region, and treatment.
ANCOVA = analysis of covariance; CI = confidence interval; Diff = difference; ITT = intent-to-treat; LS = least squares; N = number of subjects; SD = standard deviation.

A summary of the secondary efficacy results for the analyses of seizures are presented in Table 8.

Table 8. Statistical Summary of Secondary Efficacy Results – Seizures Parameters (ITT Population)

Secondary Efficacy Endpoint Value	Pregabalin 165 mg (N=100)	Pregabalin 330 mg (N=112)	Placebo (N=109)
Responder Rate, Overall			
N assessed	98	111	109
Responder, n (%)	37 (37.8)	51 (45.9)	39 (35.8)
Non-responder, n (%)	61 (62.2)	60 (54.1)	70 (64.2)
Pairwise p-value versus placebo	0.752	0.125	-
Percentage Change From Baseline in 28-Day Partial Seizure Rates, Overall[a]			
N	98	111	109
Mean (SD)	-21.24 (70.741)	-37.82 (40.240)	-12.07 (168.311)
95% CI of mean	-35.42, -7.06	-45.39, -30.25	-44.03, 19.88
Median	-38.02	-43.43	-35.35
Range	-100.0, 346.9	-100.0, 114.0	-100.0, 1650.0
LS mean (SE)	-15.00 (11.668)	-31.54 (10.772)	-5.70 (10.918)
95% CI of LS mean	-37.96, 7.96	-52.73, -10.34	-27.19, 15.78
LS mean diff (SE) versus placebo (%)	-9.30 (15.17)	-25.84 (14.64)	-
95% CI of LS mean diff (%)	-39.16, 20.56	-54.64, 2.97	-
p-Value versus placebo	0.5404	0.0786	-
Frequency of SGTC During Double-Blind Treatment Phase, Overall[b]			
N	98	111	109
Mean (SD)	3.99 (8.667)	4.43 (14.736)	7.51 (24.979)
95% CI of mean	2.25, 5.73	1.66, 7.20	2.77, 12.26
Median	0.00	0.00	1.00
Range	0.0 to 40.0	0.0 to 129.0	0.0 to 230.0
LS mean diff (SE) versus placebo	-0.11 (0.214)	-0.16 (0.191)	-
95% CI of LS mean diff	-0.53, 0.31	-0.53, 0.22	-
p-Value versus placebo	0.6073	0.4109	-
Log-Transformed 28-Day SGTC Seizure Rate for All SGTCs Collected During Double-Blind Maintenance Phase, Overall			
N	96	110	109
Mean (SD)	0.42 (0.733)	0.43 (0.707)	0.53 (0.828)
95% CI of mean	0.27, 0.56	0.29, 0.56	0.37, 0.68
Median	0.00	0.00	0.00
Range	0.0 to 2.6	0.0 to 3.6	0.0 to 4.2
LS Mean (SE)	0.46 (0.049)	0.48 (0.045)	0.48 (0.046)
95% CI of LS mean	0.37, 0.56	0.40, 0.57	0.39, 0.57
LS mean diff versus placebo (%)	-1.38	0.75	-
95% CI of LS mean diff (%)	-12.97, 11.75	-10.69, 13.66	-
p-Value versus placebo	0.8268	0.9024	-
SGTC Responder Rate Based on 50% Reduction in 28-Day SGTC Seizure Rate During the Double-Blind Treatment Phase, Overall			
N assessed	96	108	105
Responder, n (%)	1 (1.0)	2 (1.9)	2 (1.9)
Non-responder, n (%)	95 (99.0)	106 (98.1)	103 (98.1)
Pairwise p-value versus placebo	0.670	0.927	-
Log-Transformed 28-Day Seizure Rate for All Partial Except Without Motor Collected During Double-Blind Maintenance Phase, Overall			
N	96	110	109
Mean (SD)	1.79 (1.033)	1.75 (1.079)	1.84 (1.172)
95% CI of Mean	1.58, 2.00	1.54, 1.95	1.62, 2.07

Table 8. Statistical Summary of Secondary Efficacy Results – Seizures Parameters (ITT Population)

Secondary Efficacy Endpoint Value	Pregabalin 165 mg (N=100)	Pregabalin 330 mg (N=112)	Placebo (N=109)
Median	1.68	1.59	1.61
Range	0.0 to 4.6	0.0 to 4.9	0.0 to 5.2
LS Mean (SE)	1.91 (0.070)	1.77 (0.064)	1.88 (0.065)
95% CI of LS mean	1.77, 2.04	1.64, 1.89	1.76, 2.01
LS mean diff versus placebo (%)	2.28	-10.78	-
95% CI of LS mean diff (%)	-14.37, 22.15	-24.81, 5.87	-
p-Value versus placebo	0.8034	0.1905	-

Overall refers to all treatment days during the double-blind treatment phase.
CI = confidence interval; diff = difference; ITT = intent-to-treat; LS = least squares; N = number of subjects in each treatment group; n = number of subjects in specific criteria; SD = standard deviation; SE = standard error; SGTC = secondary generalized tonic-clonic.

a. Percent reduction in seizures were calculated as follows: 100% × (exp [X] – 1) = %, where X is the log value.
b. Estimates and p-values were from a generalized linear model accounting for treatment and geographic region as fixed effects and baseline seizure frequency as a covariate. This generalized linear model assumed that the SGTC seizure frequency was from a Poisson distribution with a canonical log link function.

A summary of the changes from Baseline in the HADS subscales at Week 14 is present in Table 9.

A summary of the changes from Baseline at Week 14 for the MOS-SS subscale scores is summarized in Table 10. The statistical summary of MOS-SS optimal sleep subscale is presented in Table 11.

The summary of BSW questionnaire at Week 14 is presented in Table 12.

Table 9. Summary of ANCOVA for Change From Baseline at Week 14 in HADS-A and HADS-D – (ITT Population)

HADS Subscale Treatment Group	N	Baseline Value Mean (SD)	N	Week 14 Observed Value Mean (SD)	N	Change From Baseline Mean (SD)	Treatment Comparison Versus Placebo, ANCOVA LS Mean Diff (SE)	95% CI	p-Value
HADS-A Anxiety Scale									
Pregabalin 165 mg	99	5.5 (4.27)	94	4.6 (3.93)	93	-0.8 (3.34)	-0.3 (0.41)	-1.1, 0.5	0.4650
Pregabalin 330 mg	111	5.3 (3.98)	104	4.8 (3.72)	103	-0.4 (3.19)	0.0 (0.40)	-0.8, 0.8	0.9692
Placebo	107	5.4 (4.35)	101	4.8 (3.95)	101	-0.5 (3.13)	-	-	-
HADS-D Depression Scale									
Pregabalin 165 mg	99	4.0 (3.31)	94	3.4 (3.52)	93	-0.5 (3.16)	-0.5 (0.43)	-1.3, 0.4	0.2693
Pregabalin 330 mg	111	4.3 (3.91)	104	3.6 (3.62)	103	-0.8 (3.49)	-0.5 (0.42)	-1.4, 0.3	0.1893
Placebo	107	4.1 (3.37)	101	3.9 (3.86)	101	-0.1 (3.17)	-	-	-

HADS-A: Anxiety subscale of Hospital Anxiety and Depression Scale (sum of Items 1, 3, 5, 7, 9, 11, and 13).
HADS-D: Depression subscale of Hospital Anxiety and Depression Scale (sum of Items 2, 4, 6, 8, 10, 12, and 14).
Scores from both subscales range from 0 to 21 with higher scores indicating more severe anxiety or depression (scoring can be interpreted as 0-7 normal; 8-10 mild; 11-14 moderate; and 15-21 severe).
Estimates and p-values are from an ANCOVA model including fixed effects for baseline value, region, and treatment.
ANCOVA = analysis of covariance; CI = confidence interval; Diff = difference; HADS-A = Hospital Anxiety and Depression Scale – Anxiety (subscale); HADS-D = Hospital Anxiety and Depression Scale – Depression (subscale); ITT = intent-to-treat; LS = least squares; N = number of subjects; SD = standard deviation; SE = standard error.

Table 10. Summary of ANCOVA for Change From Baseline at Week 14 in for MOS-SS Subscales (Except Optimal Sleep Subscale) (ITT Population)

Scores Treatment Group	N	Baseline Value Mean (SD)	N	Week 14 Observed Value Mean (SD)	N	Change From Baseline Mean (SD)	Treatment Comparison Versus Placebo, ANCOVA LS Mean Diff (SE)	95% CI	p-Value
Sleep Disturbance									
Pregabalin 165 mg	99	27.3 (23.78)	94	23.4 (23.37)	93	-3.9 (19.89)	-0.8 (2.24)	-5.2, 3.6	0.7347
Pregabalin 330 mg	111	22.6 (19.04)	104	21.4 (18.63)	103	-1.5 (17.93)	0.3 (2.17)	-4.0, 4.6	0.8971
Placebo	107	23.4 (23.11)	101	21.2 (21.10)	101	-1.9 (14.10)	-	-	-
Snoring									
Pregabalin 165 mg	98	21.8 (29.30)	94	18.5 (22.38)	92	-3.5 (25.44)	-2.7 (3.22)	-9.1, 3.6	0.3972
Pregabalin 330 mg	111	24.0 (29.40)	104	29.0 (32.96)	103	5.4 (26.00)	6.7 (3.12)	0.6, 12.9	0.0319
Placebo	107	22.2 (30.51)	101	20.0 (28.57)	101	-0.6 (22.71)	-	-	-
Sleep Short of Breath or Headache									
Pregabalin 165 mg	99	10.3 (18.60)	94	11.3 (20.44)	93	0.2 (20.75)	0.8 (2.62)	-4.4, 5.9	0.7708
Pregabalin 330 mg	111	11.7 (18.18)	104	13.3 (20.97)	103	1.0 (24.48)	2.4 (2.55)	-2.7, 7.4	0.3560
Placebo	107	12.1 (19.38)	101	10.3 (17.35)	101	-0.8 (18.96)	-	-	-
Quantity of Sleep (hours)									
Pregabalin 165 mg	98	7.4 (1.45)	94	7.6 (1.26)	92	0.2 (1.31)	0.2 (0.15)	-0.1, 0.5	0.1129
Pregabalin 330 mg	111	7.6 (1.30)	104	7.5 (1.40)	103	-0.1 (1.18)	0.0 (0.15)	-0.3, 0.3	0.9388
Placebo	107	7.6 (1.42)	100	7.4 (1.34)	100	-0.1 (1.25)	-	-	-
Sleep Adequacy									
Pregabalin 165 mg	99	66.7 (28.32)	94	68.8 (28.05)	93	2.3 (31.14)	-0.4 (3.60)	-7.5, 6.6	0.9053
Pregabalin 330 mg	111	69.2 (28.26)	104	69.2 (28.78)	103	-1.7 (31.44)	-1.6 (3.48)	-8.5, 5.2	0.6371
Placebo	107	73.9 (27.74)	101	73.1 (28.94)	101	-1.5 (24.55)	-	-	-
Sleep Somnolence									
Pregabalin 165 mg	99	22.8 (20.02)	94	22.3 (18.95)	93	-0.5 (17.29)	-6.4 (2.53)	-11.4, -1.4	0.0119
Pregabalin 330 mg	111	24.4 (19.83)	104	29.9 (24.30)	103	5.2 (19.42)	0.0 (2.46)	-4.9, 4.8	0.9909
Placebo	107	24.5 (20.25)	101	29.4 (24.13)	101	5.0 (18.72)	-	-	-
Sleep Problems Index I									
Pregabalin 165 mg	99	24.1 (19.10)	94	22.0 (19.27)	93	-2.2 (16.91)	-1.1 (1.98)	-5.0, 2.8	0.5903
Pregabalin 330 mg	111	22.7 (16.39)	104	22.8 (16.89)	103	0.4 (16.43)	0.7 (1.92)	-3.1, 4.5	0.7126
Placebo	107	20.8 (18.60)	101	20.6 (17.36)	101	0.3 (12.62)	-	-	-
Sleep Problems Index II									
Pregabalin 165 mg	99	25.9 (19.19)	94	23.5 (18.62)	93	-2.4 (15.62)	-2.1 (1.84)	-5.8, 1.5	0.2431
Pregabalin 330 mg	111	23.8 (15.70)	104	24.4 (17.31)	103	0.7 (14.53)	0.3 (1.78)	-3.2, 3.8	0.8654

Table 10. Summary of ANCOVA for Change From Baseline at Week 14 in for MOS-SS Subscales (Except Optimal Sleep Subscale) (ITT Population)

Scores Treatment Group	N	Baseline Value Mean (SD)	N	Week 14 Observed Value Mean (SD)	N	Change From Baseline Mean (SD)	Treatment Comparison Versus Placebo, ANCOVA LS Mean Diff (SE)	95% CI	p-Value
Placebo	107	22.7 (18.35)	101	23.0 (17.24)	101	0.7 (11.30)	-	-	-

Quantity of sleep was measured in hours.
Scores range from 0-100 with higher scores indicating greater impairment with the exception of sleep adequacy subscale.
Estimates and p-values are from an ANCOVA model including fixed effects for baseline value, region, and treatment.
ANCOVA = analysis of covariance; CI = confidence interval; Diff = difference; ITT = intent-to-treat; LS=least squares; MOS-SS = Medical Outcomes Study-Sleep Scale; N = number of subjects; SD = standard deviation.

Table 11. Summary for MOS-SS Optimal Sleep Subscale (ITT Population)

Time Point Treatment Group	N	Optimal Sleep n (%)	Non-Optimal Sleep n (%)	Treatment Differences at Week 14 N	Odds Ratio[a]	95% CI	p-Value[b]
Baseline/Week 0[c]							
Pregabalin 165 mg	93	54 (58.1)	39 (41.9)				
Pregabalin 330 mg	103	67 (65.0)	36 (35.0)				
Placebo	103	60 (58.3)	43 (41.7)				
Week 14[d]							
Pregabalin 165 mg	93	63 (67.7)	30 (32.3)	96/103	1.36	0.74, 2.50	0.3241
Pregabalin 330 mg	103	62 (60.2)	41 (39.8)	105/103	0.96	0.54, 1.71	0.8932
Placebo	103	62 (60.2)	41 (39.8)	-	-	-	-

This analysis assessed the MOS-SS relative to the start of randomized treatment and did not take into account whether the assessment was made while on monotherapy treatment.
Optimal sleep was defined as an average of 7 or 8 hours of sleep per night.
CI = confidence interval; ITT = intent-to-treat; MOS-SS = Medical Outcomes Study-Sleep Scale; N = number of subjects; n = number of subjects in specific criteria.

a. Odds ratio was the probability of the event occurring in pregabalin CR 165 mg/pregabalin CR 330 mg relative to the event occurring in placebo. Odds ratio >1 was in favor of pregabalin CR 165 mg/pregabalin CR 330 mg treatment group.
b. Nominal p-value for 2-sided test.
c. Baseline referred to Visit 3 (Week 0 – enrollment).
d. Week 14 included early terminations start taper, early terminations ending without taper, and Week 14 end of treatment start taper visits.

Table 12. Summary of Benefit, Satisfaction, and Willingness to Continue Questionnaire at Week 14 (ITT Population)

Parameter Value	Number (%) of Subjects		
	Pregabalin 165 mg (N=100)	Pregabalin 330 mg (N=112)	Placebo (N=109)
Benefit From Treatment			
No	12 (12.0)	20 (17.9)	24 (22.0)
Little benefit	31 (31.0)	26 (23.2)	36 (33.0)
Much benefit	54 (54.0)	63 (56.3)	46 (42.2)
Not done	2 (2.0)	2 (1.8)	2 (1.8)
Missing	1 (1.0)	1 (0.9)	1 (0.9)
Satisfaction From Treatment (Yes/No)			
No	13 (13.0)	20 (17.9)	26 (23.9)
Yes	84 (84.0)	90 (80.4)	80 (73.4)
Missing	3 (3.0)	2 (1.8)	3 (2.8)
Willingness to Continue (Yes/No)			
No	18 (18.0)	25 (22.3)	29 (26.6)
Yes	79 (79.0)	85 (75.9)	77 (70.6)
Missing	3 (3.0)	2 (1.8)	3 (2.8)

Week 14 included early termination ending in taper, early termination ending without taper, and Week 14 end of treatment without taper.
ITT = intent-to-treat; N = number of subjects.

Safety Results:

Treatment-emergent non-SAEs by system organ class and preferred term (all causalities) reported in >2% of subjects are presented in Table 13. Treatment-emergent non-SAEs by system organ class and preferred term (treatment-related) in >2% of subjects are presented in Table 14.

Table 13. Treatment-Emergent Non-Serious Adverse Events by System Organ Class and Preferred Term (All Causalities) in >2% of Subjects

Number (%) of Subjects With Adverse Events by System Organ Class and MedDRA (v14.1) Preferred Term	Pregabalin 165 mg n (%)/c	Pregabalin 330 mg n (%)/c	Placebo n (%)/c	Overall n (%)/c
Evaluable for adverse events	100	113	110	323
With non-serious adverse events	40 (40.0)	48 (42.5)	40 (36.4)	128 (39.6)
Eye disorders	3 (3.0)/3	4 (3.5)/4	0	7 (2.2)/7
Vision blurred	3 (3.0)/3	4 (3.5)/4	0	7 (2.2)/7
Gastrointestinal disorders	6 (6.0)/6	1 (0.9)/1	1 (0.9)/2	8 (2.5)/9
Dry mouth	3 (3.0)/3	0	1 (0.9)/1	4 (1.2)/4
Nausea	3 (3.0)/3	1 (0.9)/1	1 (0.9)/1	5 (1.5)/5
General disorders and administration site conditions	3 (3.0)/3	6 (5.3)/6	1 (0.9)/1	10 (3.1)/10
Fatigue	3 (3.0)/3	6 (5.3)/6	1 (0.9)/1	10 (3.1)/10
Investigations	1 (1.0)/1	7 (6.2)/7	0	8 (2.5)/8
Weight increased	1 (1.0)/1	7 (6.2)/7	0	8 (2.5)/8
Metabolism and nutrition disorders	0	3 (2.7)/3	0	3 (0.9)/3
Increased appetite	0	3 (2.7)/3	0	3 (0.9)/3
Nervous system disorders	15 (15.0)/19	16 (14.2)/24	5 (4.5)/7	36 (11.1)/50
Dizziness	11 (11.0)/14	11 (9.7)/15	2 (1.8)/2	24 (7.4)/31
Headache	1 (1.0)/1	3 (2.7)/4	3 (2.7)/3	7 (2.2)/8
Somnolence	4 (4.0)/4	5 (4.4)/5	2 (1.8)/2	11 (3.4)/11
Vascular disorders	0	3 (2.7)/3	0	3 (0.9)/3
Hypertension	0	3 (2.7)/3	0	3 (0.9)/3

n = Number of subjects with events. Subjects were counted once per treatment for each row.
c = Number of events. Events were counted once for each occurrence per subject per treatment for each row.
Includes data up to 28 days after last dose of study drug.
MedDRA (v14.1) coding dictionary applied.
MedDRA = Medical Dictionary for Regulatory Activities; v = version.

Table 14. Treatment-Emergent Non-Serious Adverse Events by System Organ Class and Preferred Term (Treatment-Related) in >2% of Subjects

Number (%) of Subjects With Adverse Events by: System Organ Class and MedDRA (14.1) Preferred Term	Pregabalin 165 mg n (%)	Pregabalin 330 mg n (%)	Placebo n (%)	Overall n (%)
Evaluable for adverse events	100	113	110	323
With adverse events	18 (18.0)	22 (19.5)	6 (5.5)	46 (14.2)
Any adverse event	18 (18.0)	22 (19.5)	6 (5.5)	46 (14.2)
Eye disorders	3 (3.0)	4 (3.5)	0	7 (2.2)
Vision blurred	3 (3.0)	4 (3.5)	0	7 (2.2)
Gastrointestinal disorders	3 (3.0)	0	1 (0.9)	4 (1.2)
Dry mouth	3 (3.0)	0	1 (0.9)	4 (1.2)
General disorders and administration site conditions	3 (3.0)	6 (5.3)	1 (0.9)	10 (3.1)
Fatigue	3 (3.0)	6 (5.3)	1 (0.9)	10 (3.1)
Investigations	1 (1.0)	7 (6.2)	0	8 (2.5)
Weight increased	1 (1.0)	7 (6.2)	0	8 (2.5)
Nervous system disorders	14 (14.0)	12 (10.6)	4 (3.6)	30 (9.3)
Dizziness	11 (11.0)	9 (8.0)	2 (1.8)	22 (6.8)
Somnolence	3 (3.0)	4 (3.5)	2 (1.8)	9 (2.8)

Subjects were only counted once per treatment for each row.
Includes data up to 28 days after last dose of study drug.
MedDRA (v14.1) coding dictionary applied.
MedDRA = Medical Dictionary for Regulatory Activities; n = number of subjects in specified criteria; v = version.

Serious Adverse Events: The number of occurrences for treatment-emergent SAEs by system organ class and preferred term (all causalities and treatment-related) are presented in Table 15.

Table 15. Number of Occurrences for Treatment-Emergent SAEs by System Organ Class and Preferred Term (All Causalities and Treatment-Related) (Safety Population)

Number of Subjects Evaluable for AEs System Organ Class Preferred Term	Pregabalin 165 mg (N=100) n/c	 n[a]/c[b]	Pregabalin 330 mg (N=113) n/c	 n[a]/c[b]	Placebo (N=110) n/c	 n[a]/c[b]	Overall (N=323) n/c	 n[a]/c[b]
Number of subjects/occurrences of SAEs	5/7	0/0	5/7	2/4	2/2	0/0	12/16	2/4
Infections and infestations	3/3	0/0	1/1	0/0	0/0	0/0	4/4	0/0
Bronchitis	1/1	0/0	0/0	0/0	0/0	0/0	1/1	0/0
Pneumonia	1/1	0/0	0/0	0/0	0/0	0/0	1/1	0/0
Subcutaneous abscess	0/0	0/0	1/1	0/0	0/0	0/0	1/1	0/0
Viral infection	1/1	0/0	0/0	0/0	0/0	0/0	1/1	0/0
Injury, poisoning and procedural complications	0/0	0/0	0/0	0/0	1/1	0/0	1/1	0/0
Wound	0/0	0/0	0/0	0/0	1/1	0/0	1/1	0/0
Nervous system disorders	3/4	0/0	3/4	2/3	1/1	0/0	7/9	2/3
Ataxia	0/0	0/0	1/1	1/1	0/0	0/0	1/1	1/1
Complex partial seizures	1/1	0/0	0/0	0/0	0/0	0/0	1/1	0/0
Convulsion	1/1	0/0	1/1	0/0	1/1	0/0	3/3	0/0
Epilepsy	1/1	0/0	0/0	0/0	0/0	0/0	1/1	0/0
Grand mal convulsion	1/1	0/0	0/0	0/0	0/0	0/0	1/1	0/0
Myoclonus	0/0	0/0	1/1	1/1	0/0	0/0	1/1	1/1
Somnolence	0/0	0/0	1/1	1/1	0/0	0/0	1/1	1/1
Psychiatric disorders	0/0	0/0	2/2	1/1	0/0	0/0	2/2	1/1
Anxiety	0/0	0/0	1/1	1/1	0/0	0/0	1/1	1/1
Hallucination	0/0	0/0	1/1	0/0	0/0	0/0	1/1	0/0

n = The number of subjects for each SAE (all causalities); c = The number of occurrences for each SAE (all causalities).
MedDRA (v14.1) coding dictionary applied.
AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; N = total number of subjects in specified criteria; SAE = serious adverse event; v = version.

a. The number of subjects for each SAE (treatment-related).
b. The number of occurrences for each SAE (treatment-related).

Permanent Discontinuations due to Adverse Events: A total of 14 subjects permanently discontinued treatment due to AEs: 3 subjects (3%) in the pregabalin CR 165 mg treatment group, 8 subjects (7.1%) in the pregabalin CR 330 mg treatment group, and 3 subjects (2.7%) in the placebo treatment group. Treatment-emergent AEs resulting in permanent discontinuation were as follows: oedema peripheral (3 subjects); weight increased (2 subjects); somnolence (2 subjects); ecchymosis, vomiting, ataxia, myoclonus, disturbance in attention, anxiety, depression, flat affect, fatigue, convulsion, epilepsy, and drug eruption (1 subject each).

Dose Reductions or Temporary Discontinuations due to Adverse Events: A total of 5 subjects reported temporary treatment discontinuation due to AEs (2 subjects in the pregabalin CR 165 mg treatment group and 3 subjects in the pregabalin CR 330 mg treatment group) and in 2 subjects (both in the pregabalin 165 mg group) dose was reduced due to AEs.

AEs leading to temporary treatment discontinuation were as follows: urinary retention, bronchitis, nasopharyngitis, balance disorder, dizziness, hypertension, and insomnia (1 subject each).

AEs leading to dose reductions were as follows: diplopia, dizziness, and urinary tract infection (1 subject each).

Deaths: There was 1 death (due to status epilepticus) reported during the study which occurred prior to randomization.

Laboratory Values Over Time: Overall, 30 of 99 subjects in the pregabalin CR 165 mg treatment group, 32 of 111 subjects in the pregabalin CR 330 mg treatment group, and 36 of 108 subjects in the placebo treatment group who were evaluable for laboratory abnormalities experienced a laboratory abnormality during the study.

Vital Signs: Weight, heart rate, and systolic and diastolic BP were examined for clinically important changes from Baseline to Week 14/ Early Termination (ET); there were no clinically meaningful findings.

Physical Examination: There were no clinically significant physical examination findings at Baseline or at the End of Treatment.

Electrocardiogram: There were no clinically significant ECG findings at Screening or at Visit 8/ET.

Neurological Examination: There were no clinically significant neurological examination findings at Baseline or at Week 14.

Suicidal Ideation and Behavior Assessment: There were 4 subjects in the pregabalin CR 165 mg treatment group, 3 subjects in the pregabalin CR 330 mg treatment group, and 2 subjects in the placebo group that reported suicidal ideation after initiation of study treatment. There were no post-baseline suicidal behaviors reported in any group.

CONCLUSIONS:

A statistically significant difference between the pregabalin CR 330 mg treatment group versus the placebo treatment group for the primary efficacy endpoint of log-transformed (log_e) 28-day seizure rate for all partial onset seizures collected during the double-blind treatment phase was not demonstrated. Since the first step in the pre-defined sequential testing procedure primary analysis failed to reject the null hypothesis, further testing was stopped and no treatment effect was claimed.

There were no treatment group differences between either of the 2 pregabalin treatment groups versus the placebo treatment group for any of the seizure-related secondary efficacy endpoints, or for the change from Baseline in HADS-A, HADS-D, and most MOS-SS subscales, with the exception of sleep somnolence and snoring in the pregabalin CR 165 mg and pregabalin CR 330 mg treatment groups, respectively.

Pregabalin CR demonstrated an acceptable safety and tolerability profile. Pregabalin CR was well-tolerated and the AE reports were consistent with the known safety profile of pregabalin.