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GENERIC DRUG NAME and/or COMPOUND NUMBER: Pregabalin / PD-144,723

PROTOCOL NO.: A0081157

PROTOCOL TITLE: A Randomized, Double-Blind, Parallel-Group, Multi-center, Comparative Flexible-Dose Study of Pregabalin Versus Levetiracetam as Adjunctive Therapy to Reduce Seizure Frequency in Subjects With Partial Seizures

Study Centers: A total of 71 sites in 21 countries took part in the study and enrolled subjects: Czech Republic, Republic of Korea, Philippines (7 centers each); Spain (6 centers); Bulgaria (5 centers); Russian Federation, Italy (4 centers each); Colombia, India, Lithuania, Taiwan, Turkey (3 centers each); Belgium, Costa Rica, France, Germany, Greece, Mexico, Peru (2 centers each); and Panama, Venezuela (1 center each).

Study Initiation and Completion Dates: 31 October 2007 to 22 May 2012

Phase of Development: Phase 3b

Study Objectives:

Primary objective: To compare the efficacy of pregabalin and levetiracetam, at doses up to the maximal ones used in pivotal registration trials, as adjunctive therapy in subjects with refractory partial seizures, under randomized, parallel-group, flexible-dose conditions.

Secondary objectives: To evaluate the safety and tolerability of pregabalin and levetiracetam in this subject population.

METHODS

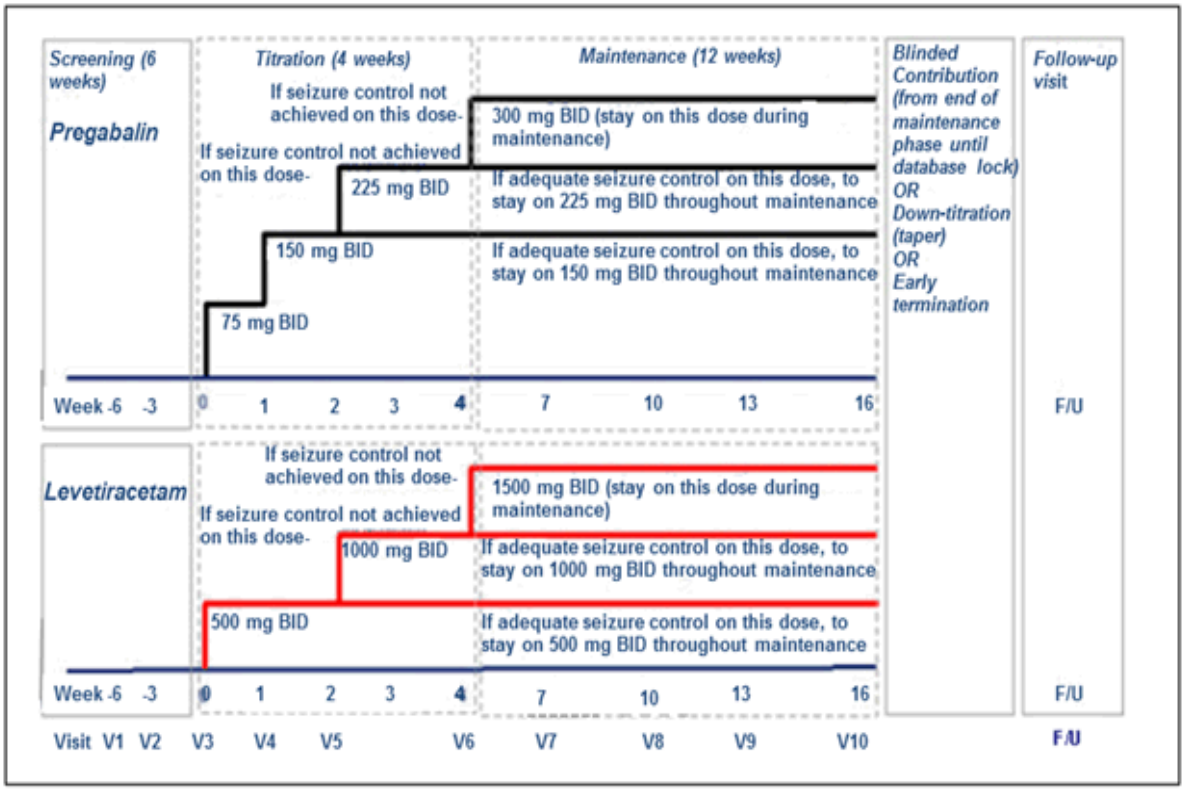
Study Design: This was a randomized, double-blind, double-dummy, flexible-dose, 2-arm, parallel-group study in subjects with refractory partial seizures.

The study was comprised of 4 phases: (1) a 6-week screening period leading to (2) a 4-week titration phase; once a final dose of medication had been achieved, (3) a 12-week maintenance treatment phase; following this, subjects either entered (4) a blinded continuation phase, or had study medication discontinued (Figure 1).

Following randomization (1:1 ratio), eligible subjects returned for outpatient visits every 1 to 3 weeks until completion of the 4-week titration and 12-week maintenance phases. Subjects who completed the maintenance phase and who entered the blinded continuation phase had outpatient visits every 6 months for a maximum of 2 years in blinded continuation or until

the last subject either completed or discontinued from the maintenance phase of the study, whichever was earlier. For subjects who did not enter the blinded continuation phase, blinded study medication was down-titrated over 1 week. After study completion, subsequent treatment was based on the clinical judgment of the individual subject's physician. A schedule of activities is presented in Table 1.

Figure 1. Study Design Diagram



BID = twice daily, F/U = follow-up, V = visit.

Table 1. Schedule of Activities

Study Periods and Follow-Up	Baseline Phase Screening		Double-Blind Titration Phase				Double-Blind Maintenance Phase				Continuation Phase[a]	Follow-up Visit[b]
			R									
Clinic Visit Number	**V1**	**V2**	**V3[c,d]**	**V4**	**V5**	**V6[e]**	**V7**	**V8**	**V9**	**V10/Term[c,f,g]**		**F/U[c]**
End of weeks in study	-6	-3	0	1	2	4	7	10	13	16	At 6 month intervals	7 days post taper
Study day (±3 days)	-42	-21	0	7	14	28	49	70	91	112	168 (±13 days)	
Informed consent	X											
Inclusion/exclusion criteria	X	X	X									
Medical history	X											
Epilepsy-related history	X											
Demographics	X											
Physical/neurological examination	X									X		X
Diagnostic review form[h]			X									
Seizure identification form[h]			X									
Review and record seizures	X	X	X	X	X	X	X	X	X	X	X	X
Concurrent medication recording	X	X	X	X	X	X	X	X	X	X	X	X
ECG	X									X		
BPRS	X						X	X	X	X		X
HADS	X									X		
MOS-sleep scale	X									X		
Pregnancy test[i]	X		X				X			X	X	X
Vital signs and body weight[j]	X	X	X	X	X	X	X	X	X	X	X	X
Clinical laboratory tests[k]	X		X		X		X			X		X
Study medication dispensing/dosing			X[d]	X	X	X	X	X	X	X	X[l]	X[m]
Adverse events recording		X	X	X	X	X	X	X	X	X	X	X

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Study Periods and Follow-Up	Baseline Phase Screening		Double-Blind Titration Phase				Double-Blind Maintenance Phase				Continuation Phase[a]	Follow-up Visit[b]
			R									
Clinic Visit Number	V1	V2	V3[c,d]	V4	V5	V6[e]	V7	V8	V9	V10/Term[c,f,g]		F/U[c]

BPRS = Brief Psychiatric Rating Scale; ECG = electrocardiogram; F/U = follow-up, HADS = Hospital Anxiety and Depression Scale; MOS = Medical Outcomes Study; R = randomization, V = visit.

a. Subjects who had shown clinical benefit were eligible to continue in the blinded continuation phase of the study. During the blinded continuation phase of the study, visits occurred every 6 months from Visit 10 for a maximum of 2 years in blinded continuation or until the last subject either completed or discontinued from the maintenance phase of the study, whichever was earlier. When a subject discontinued during blinded continuation, all of these assessments were followed and the taper was dispensed. The F/U visit was to be conducted after 7 days. During blinded continuation it may have been necessary for subjects to be dispensed medication at 3 month intervals; however, the full set of assessments was only to be performed every 6 months.

b. All subjects had a F/U Visit. For subjects who did not consent to enter the blinded continuation phase of the study, there was a down-titration of blinded study medication over 1 week, starting after Week 16. Subsequent treatment was based on the clinical judgment of the subject's physician. Subjects may have needed to return to the site more frequently to be resupplied with study medication.

c. The taper was not applicable to subjects who terminated the study between Visit 3 and Visit 4. If the subject discontinued between Visit 3 and Visit 10, then all the assessments at Visit 10 were to be performed. If the subject discontinued after Visit 10 (during blinded continuation), then all the activities listed under F/U visit were to be performed.

d. Subjects began study medication the morning following Visit 3 (Study Day 1).

e. Visit 6 was the last visit of the double-blind titration phase and the first visit of the double-blind maintenance phase.

f. These procedures were also performed for subjects withdrawing early from the study.

g. Visit 10 was the start taper visit for subjects who elected not to enter blinded continuation and for subjects who terminated early (early termination). Visit 10 could also have been the visit for the start of blinded continuation if the subject continued in the study in blinded continuation.

h. The diagnostic review form and the seizure identification form were to be submitted for randomized subjects only. They were not required for screen failures.

i. Serum pregnancy tests were performed at Visit 1. All other pregnancy tests were urine pregnancy tests, unless the urine pregnancy test was positive, which should then have been confirmed with a serum pregnancy test.

j. As far as practical, weight measurements were standardized using a hospital-quality scale. Subjects were weighed without shoes, and with a consistent level of clothing.

k. All laboratory tests were to be fasted.

l. Dispense dose tapering or continuation phase medication.

m. At the F/U visit, the study drug was returned and the study drug dosing was reviewed and recorded.

Number of Subjects (Planned and Analyzed): It was planned to screen approximately 814 subjects and to randomize 570 subjects, ie., the calculated sample size to obtain 400 per-protocol (PP) subjects, with 200 evaluable subjects per arm (assuming a 30% screen failure and a 30% dropout rate). Overall, 633 subjects were screened and 509 subjects participated in the study: 254 subjects in the pregabalin group and 255 subjects in the levetiracetam group.

Diagnosis and Main Criteria for Inclusion: Male or nonpregnant nonlactating female subjects ≥18 years of age, with a diagnosis of epilepsy with partial seizures, as defined in the International League Against Epilepsy classification of seizures, who had diagnosis of epilepsy for ≥2 years, and were unresponsive to treatment with ≥2 (but ≤5) prior antiepileptic drugs (AEDs), and at the time of study enrollment were on stable dosages of 1 or 2 standard AEDs. The subjects were required to have had magnetic resonance imaging or contrast enhance computed tomography scan of the brain that demonstrated no progressive structural central nervous system abnormality since the time of the diagnosis of epilepsy, and a electroencephalograph (EEG) testing done within 2 years of randomization, and EEG abnormalities were be consistent with a diagnosis of focal-onset epilepsy. During the 6-week baseline period, subjects had to have had a minimum of 4 partial seizures, with no 28-day period free of partial seizures with or without secondary generalization. A caregiver or witness had to be with the subject for a sufficient duration to accurately chronicle the occurrence of seizures, which had to be documented in the subject's diary.

Excluded were subjects with other neurologic illness that could impair endpoint assessment, or subjects with Lennox-Gastaut syndrome, absence seizures, status epilepticus within the 12 months prior to enrollment, or with seizures due to an underlying medical illness or metabolic syndrome, females who were pregnant, breast feeding, or intend to become pregnant during the course of the trial, a history of lack of response to or hypersensitivity or poor tolerability with levetiracetam or pregabalin, previous use of levetiracetam (less than one month), gabapentin or pregabalin within 30 days prior to randomization, or likelihood of engaging in these treatments during the study period.

Study Treatment: Study treatments were administered using a double-blind, double-dummy approach. Subjects received 2 sets of blinded clinical supplies during the study: (1) active levetiracetam and placebo pregabalin, or (2) active pregabalin and placebo levetiracetam. Randomized subjects entered a 4-week double-blind titration phase to establish an individualized dose of either of the active study medications (ie, pregabalin or levetiracetam); this established dose was taken forward into a 12-week maintenance phase of the study (Weeks 4 to 16). At the end of the maintenance phase, subjects had an opportunity to progress into the blinded continuation phase, with complete follow-up visits every 6 months (in addition, subjects may have returned to the site every 3 months for dispensation of study medication). Study medication was dispensed in bottles via the tele-randomization system. All subjects were instructed to take their study medication twice a day, once in the morning and once at night beginning the morning following Visit 3 (Study Day 1). The treatments used in this study were as follows.

Pregabalin capsules 150 mg/day to 600 mg/day flexible optimized dose of 150 mg/day (75 mg capsules twice daily [BID]); or 300 mg/day (150 mg capsules BID); or 450 mg/day (225 mg capsules BID); or 600 mg/day (300 mg capsules BID); and a matching placebo.

Levetiracetam tablets 1000 mg/day to 3000 mg/day flexible optimized dose of 1000 mg/day (500 mg capsules BID); or 2000 mg/day (2 × 500 mg capsules BID); or 3000 mg/day (3 × 500 mg capsules BID); and a matching placebo.

Efficacy Endpoints:

Primary Efficacy Parameter:

The primary efficacy parameter was the responder rate, defined as the proportion of subjects who had at least 50% reduction in 28-day total partial seizure rate during the maintenance phase as measured from baseline (data collected during the screening period). Seizures were recorded on a daily seizure paper-based diary that could be completed by subjects, family members, caregivers or legal guardians. Total partial seizure was defined as the total number of (simple partial seizure + complex partial seizure + secondary generalized tonic-clonic [SGTC] seizure). Subjects who had ≥50% reduction in seizure frequency from baseline to maintenance phase were considered as responders.

Secondary Efficacy Parameters:

- Change in seizure count frequency from baseline to endpoint, calculated as the percent change in 28-day seizure frequency during the maintenance phase of treatment compared with baseline, based on the seizure diary;

- Change in frequency of SGTC seizures; change in SGTC = (proportion of SGTC/all partial seizure $rate_{db}$) - (proportion of SGTC/all partial seizure $rate_{b}$). Where (b) and (db) indicates 28-day seizure at baseline and double-blind phase, respectively. Negative values indicated reduction from baseline. Proportion of SGTC/all partial seizures was defined as SGTC 28-day rate divided by the all partial 28-day rate, calculated for both baseline and double-blind treatment (titration +maintenance) phase, based on seizure diary.

- Seizure-free rate, based on the seizure diary; where seizure free for 28 days was defined as subjects who have not had any seizure for at least 28 consecutive days from their last seizure until the end of the maintenance phase.

- Brief Psychiatric Rating Scale -Anchored version (BPRS-A); where BPRS-A was a clinician administered scale comprised of 18 items that rate severity of psychopathology on a 7-point integer scale of increasing severity from 1 (not reported) to 7 (very severe). The scale includes 10 subjectively rated items that have an additional score (9) to indicate not assessed (or not evaluable). A total score may be calculated by summing all 18 items, and a core score (psychosis cluster) can be calculated by using the sum of the items of conceptual disorganization (item 4), suspiciousness (item 11), hallucinatory behavior (item 12), and unusual thought content (item 15). Core score (psychosis cluster) was

consistent with the Positive and Negative Syndrome Scale-derived BPRS Core score (psychosis cluster). BPRS total score was ranging from 18 to 126 and higher scores indicate more impairment.

- Hospital Anxiety and Depression Scale (HADS); a 14-item self-report scale that produced separate subscale scores measuring anxiety and depression. Each subscale consisted of 7 statements, rated on a 4 point Likert-type scale from 0 (no anxiety or depression) to 3 (severe feelings of anxiety or depression). Subscale scores range from 0 to 21. Higher scores denoted greater severity of depression or anxiety.

- Medical Outcomes Study (MOS) Sleep Scale (SS) to assess sleep quality and quantity. It was a subject-rated questionnaire consisting of 12 items that assess the key constructs of sleep over the past week. The MOS-SS yielded 7 subscales (sleep disturbance, snoring, awakening short of breath or with a headache, quantity of sleep, optimal sleep, sleep adequacy, and somnolence) and a 9 item overall sleep problems index will also be calculated. The quantity of sleep subscale score was ranging from 0 to 24, indicating the number of hours of sleep. The optimal sleep score was a dichotomous 'Yes' or 'No' rating, where 'Yes' indicates optimal sleep (average 7-8 hours per night) and 'No' indicates not optimal sleep. The remaining subscales (sleep disturbance, snoring, awaken short of breath, adequacy of sleep and somnolence) and the overall sleep problems index produce scores that range from 0 to 100. Higher scores indicated greater impairment/more of a problem (negative changes thereby indicate improvement) for all except the adequacy of sleep subscale where a higher score indicates less impairment/more adequate sleep (positive changes thereby indicate improvement).

Safety Evaluations: All subjects who had taken at least 1 dose of study medication (intent-to-treat population [ITT]) were included in the evaluation for safety. Safety evaluations included monitoring of adverse events (AE) data (occurrence, nature, intensity, and relationship to study drug), clinical laboratory data, and the results of physical examinations, vital signs measurements, neurological examinations, and electrocardiograms (ECGs).

Statistical Methods:

Full Analysis Set (FAS/ITT): All randomized subjects who were administered at least 1 blinded dose of study medication, and for whom baseline and at least 1 post baseline primary efficacy evaluation was obtained were included in this population. Subjects were analyzed according to randomized treatment assignment regardless of which treatment they actually were administered. Analysis of all secondary endpoint was based on this population.

PP: The primary population was the PP population and defined as all randomized subjects who had at least 28 days of study medication during the maintenance phase and a minimum of 28 days of utilizable seizure diary data during baseline and maintenance phase of the study and did not have major protocol violation.

Safety Analysis Set: All randomized subjects who were administered at least 1 dose of double-blind study medication and provided any follow-up safety information were included in this population.

SGTC Population: Any subjects who had at least 1 intensity and relationship to study drug.

Primary Efficacy Analysis: The primary efficacy parameter was the responder rate which was calculated by the formula as described below:

> 28-day seizure rate=([Number of seizure in time {phase}]÷[Number of days in time {phase}]–[# of missing diary in time {phase}])×28

The primary analysis was performed on data from the PP population, defined as all randomized subjects who had at least 28 days of study medication during the double-blind maintenance phase, a minimum of 28 days of utilizable seizure diary data during baseline (screening) and during the maintenance phase of the study, and who did not have any major protocol violations. Data from before and after the interim analysis periods were combined for the final analysis using a weighted Z-score method.

Secondary Efficacy Analyses: Test of superiority was conducted for all secondary endpoints. Rank analysis of covariance (ANCOVA) model was used with treatment as the main effect and cluster as the cofactor. Percent change in 28-day seizure counts between the baseline and treatment periods was the dependent variable. Percent of SGTC responders and seizure free rates was analyzed using Fisher's Exact Test, if sample sizes required. ANCOVA model was used with treatment and cluster as main effects to analyze BPRS, MOS-Sleep Scale, and HADS parameters.

Safety Analysis: All safety and demographic data were summarized for all subjects receiving at least 1 dose of study medication. All AEs and serious AEs (SAEs) that occurred during the study after a subject had received the first dose of study medication were analyzed based on the standard treatment-emergent adverse event (TEAE) algorithm. All AEs (serious and non-serious) reported from the first day of study treatment were considered TEAEs. Summary tables presented the number of subjects observed with TEAEs and corresponding percentages. Within each table, the AEs were categorized by Medical Dictionary for Regulatory Activities (MedDRA) version 15.1 body system and preferred term. Additional subcategories were based on event intensity and relationship to study drug.

Summary tables were prepared to examine the distribution of laboratory measures over time. Concomitant medications were summarized using the World Health Organization-drug coding dictionary. In addition, concomitant nondrug treatments/procedures were summarized using the MedDRA coding dictionary. Descriptive statistics were provided for vital signs and weight at each assessment time. Summary of physical examination, neurological examination, and individual subject data listings were provided.

RESULTS

Subject Disposition and Demography: Subject evaluation groups through blinded continuation phase and maintenance phase are summarized in Table 2. Subject disposition

throughout the study is summarized in Table 3. Overall, 633 subjects were screened and 509 subjects participated in the study; 254 subjects in the pregabalin group and 255 subjects in the levetiracetam group. Of these, 28 (11.0%) and 19 (7.5%) subjects in the pregabalin and levetiracetam groups, respectively discontinued during the titration phase. The 462 subjects who completed the titration phase entered the maintenance phase (226 and 236 subjects in the pregabalin and levetiracetam groups, respectively). Of these, 208 (81.9%) and 210 (82.4%) subjects in the pregabalin and levetiracetam groups, respectively completed the maintenance phase; 18 and 26 subjects in the pregabalin and levetiracetam groups, respectively, discontinued during the maintenance phase.

In total, 380 (74.6%) subjects entered the blinded continuation phase (185 and 195 subjects in the pregabalin and levetiracetam groups, respectively). Of these, 80 (31.5%) and 82 (32.2%) subjects in the pregabalin and levetiracetam groups, respectively completed the continuation phase.

Table 2. Subject Evaluation Groups

		Pregabalin (N=254)	**Levetiracetam (N=255)**
		n (%)	n (%)
Number of subjects screened	633		
Assigned to study treatment		254	255
Treated		254	255
Completed the 12 week maintenance phase of the study		208 (81.9)	210 (82.4)
Discontinued during titration or maintenance phase		46 (18.1)	45 (17.6)
Completed the study[a]		80 (31.5)	82 (32.2)
Discontinued the study[b]		174 (68.5)	173 (67.8)

N = number of subjects from safety population under each treatment group; n = number of subjects analyzed in a reporting criteria.
a. Completed maintenance and blinded continuation phase of the study.
b. Discontinued during blinded continuation phase (this includes all subjects who discontinued throughout the study plus subjects who did not enter blinded continuation phase).

Table 3. Subject Disposition

	Pregabalin (N=254)	Levetiracetam (N=255)
	n (%)	n (%)
Entered titration phase	254 (100.0)	255 (100.0)
Discontinued titration phase	28 (11.0)	19 (7.5)
Completed titration phase	226 (89.0)	236 (92.5)
Entered maintenance phase	226 (89.0)	236 (92.5)
Discontinued maintenance phase	18 (7.1)	26 (10.2)
Completed maintenance phase	208 (81.9)	210 (82.4)
Withdrawn after maintenance phase but prior to blinded continuation phase	23 (9.1)	15 (5.9)
Entered blinded continuation phase	185 (72.8)	195 (76.5)
Discontinued blinded continuation phase	105 (41.3)	113 (44.3)
Completed blinded continuation phase	80 (31.5)	82 (32.2)

Percentages were calculated in reference to N.
The participation in blinded continuation phase was optional.
N = number of subjects from safety population under each treatment group; n = number of subjects analyzed in a reporting criteria.

Demographic characteristics were similar in the 2 treatment groups. Majority of subjects were females (134/254 and 130/255 in the pregabalin and levetiracetam groups, respectively). The mean (standard deviation [SD]) age of population was 32.7 (11.2) and 36.3 (12.2) years in the pregabalin and levetiracetam groups, respectively. In the pregabalin group, majority of subjects were Asian (105 [41.3%] subjects followed by White (103 [40.6%] subjects). In the levetiracetam group, majority of subjects were White (114 [44.7%] subjects) followed by Asian (87 [34.1%] subjects).

Efficacy Results:

Primary Efficacy Analysis: There were 164 and 177 PP evaluable subjects in the pregabalin and levetiracetam groups, respectively. Of these, 97 (59.0%) subjects in the pregabalin group and 104 (59.0%) subjects in the levetiracetam group had a 50% or greater reduction in 28-day seizure rate during the maintenance phase, as measured from baseline. The difference (90% confidence interval [CI]) between pregabalin and levetiracetam with respect to the rate of subjects with a 50% or more reduction in 28-day seizure rate during the maintenance phase was 0.00 (-0.08, 0.09). The non-inferiority of pregabalin as compared to levetiracetam was demonstrated with respect to the primary endpoint. The lower limit of the 90% CI for the treatment difference (pregabalin-levetiracetam) in the PP analysis set was approximately -8% which was greater than the pre-defined non-inferiority margin of approximately -12% and weighted Z-score was 2.322. Results of this analysis are presented in Table 4.

Table 4. Primary Endpoint: Weighted Z-Score: Summary of Seizure Response (50% Reduction in 28-Day Seizure Rate From Baseline to Maintenance Phase) - All Partial Seizures - PP Population

Analysis	Treatment Group	n	Number of Responders	Proportion of Responders	Difference (PGB-LEV) in Proportion of Responders
Final analysis	Pregabalin	164	97	0.59	0.00
	Levetiracetam	177	104	0.59	

Analysis	Difference (PGB-LEV) in Proportion of Responders (SE)	90% CI	Weighted Z-Score	
			Non-Inferiority	Superiority
Weighted Z-Score test	0.00 (0.05)	(-0.08, 0.09)	2.322	0.073

Z-scores and CI are calculated based on John Lawrence and HM James Hung method for combined interim and final analysis.
For non-inferiority test null hypothesis H0: P(PGB)-P(LEV) ≤ -0.12 was tested vs. alternative hypothesis H1: P(PGB)-P(LEV) > -0.12.
For superiority test null hypothesis H0: P(PGB)-P(LEV)=0 was tested vs. alternative hypothesis H1: P(PGB)-P(LEV)<>0.
P(PGB), P(LEV) - Proportion of responders in Pregabalin and Levetiracetam group, respectively.
CI = Confidence Interval for difference (PGB-LEV) estimate; n = sample size at analysis; PP = per protocol; SE = standard error; vs = versus.

The proportion of responders was >50% for all partial seizures as summarized in Table 5 for the PP population.

Table 5. Summary of Seizure Response (50% Reduction in 28-Day Seizure Rate From Baseline to Maintenance Phase) by Seizure Type - All Partial Seizures-PP Population

Seizure Type	Pregabalin (N=164)	Levetiracetam (N=177)
All partial seizure		
Response (%)	97 (59.1)	104 (58.8)
No response (%)	67 (40.9)	73 (41.2)
95% CI	(51.6, 66.7)	(51.5, 66.0)

If change from baseline to maintenance in 28-day seizure rate ≥ 50% then response = 1 (yes) otherwise response=0 (no response).
Percentages were calculated in reference to N.
CI was reported for the percentage of responders.
CI = confidence interval; N = number of PP subjects under each treatment group; PP = per protocol.

Secondary Efficacy Analysis:

There was no significant difference between treatments for the key secondary endpoint of percent change from baseline in 28-day seizure rate during the double-blind phase (titration phase + maintenance phase). The median difference (pregabalin-levetiracetam) and 95% CI in percent change from baseline in 28-day seizure rate was 4.1 (-2.6, 10.9) with a p-value of 0.3571 (Table 6).

Table 6. Summary of Treatment Differences and Ranked ANCOVA for Percent Change From Baseline to Double Blind Phase in 28-Day Seizure Rate - All Partial Seizures - FAS Population

			Treatment Differences[a]	
Treatment Comparisons	**N[b]**	**Median[c]**	**95% CI[c]**	**p-valued**
Pregabalin versus Levetiracetam	253/254	4.1	(-2.6, 10.9)	0.3571

Double blind phase refers to titration and maintenance phases.
ANCOVA = analysis of covariance; CI = confidence interval; FAS = full analysis set; N = sample size at analysis.
a. Based on treatment differences for percent change from baseline.
b. N for Pregabalin/N for Levetiracetam. N is the number of FAS subjects under each treatment group.
c. Median Differences and 95% CI were based on Hodges-Lehmann estimation.
d. p-Value was based on Ranked ANCOVA.

Distribution of percent change from baseline to double-blind phase in 28-day seizure rate for the FAS population is summarized for all partial seizures, simple partial seizures, complex partial seizures, and SGTC seizures in Table 7. Overall, 208 (82.3%) and 207 (81.5%) subjects (FAS population) in the pregabalin and levetiracetam groups, respectively had some decreases ranging from >0% to 100% in 28-day seizure rate from baseline to double-blind phase for all partial seizures. Of these, most of subjects (69 [27%] and 84 [33%] subjects in the pregabalin and levetiracetam groups, respectively) had 75% to 100% decreases.

Less than 20% subjects in the pregabalin and levetiracetam groups, respectively, had 0 to 75% increases in 28-day seizure rate for all partial seizures. Of these, the majority of subjects (19 subjects in each group) had <25% increase.

Table 7. Distribution of Percent Change From Baseline to Double Blind Phase in 28-Day Seizure Rate - FAS Population

Percent Change in 28-Day Seizure Rate	Pregabalin (N=253) n (%)	Levetiracetam (N=254) n (%)
All partial seizures		
Total	253	254
Decrease		
-100 to <75	69 (27.3)	84 (33.1)
-75 to <-50	68 (26.9)	60 (23.6)
-50 to <-25	45 (17.8)	41 (16.1)
-25 to <0	26 (10.3)	22 (8.7)
Increase		
0 to <25	19 (7.5)	19 (7.5)
25 to <50	7 (2.8)	9 (3.5)
50 to <75	3 (1.2)	7 (2.8)
≥75	16 (6.3)	12 (4.7)
Simple partial seizure		
Total	108	122
Decrease		
-100 to <-75	31 (28.7)	53 (43.4)
-75 to <-50	27 (25.0)	20 (16.4)
-50 to <-25	14 (13.0)	12 (9.8)
-25 to <0	14 (13.0)	9 (7.4)
Increase		
0 to <25	1 (0.9)	11 (9.0)
25 to <50	2 (1.9)	6 (4.9)
50 to <75	2 (1.9)	4 (3.3)
≥75	17 (15.7)	7 (5.7)
Complex partial seizure		
Total	183	184
Decrease		
-100 to <-75	65 (35.5)	78 (42.4)
-75 to <-50	50 (27.3)	43 (23.4)
-50 to <-25	19 (10.4)	14 (7.6)
-25 to <0	17 (9.3)	11 (6.0)
Increase		
0 to <25	15 (8.2)	11 (6.0)
25 to <50	3 (1.6)	8 (4.3)
50 to <75	3 (1.6)	7 (3.8)
≥75	11 (6.0)	12 (6.5)
Secondarily generalized tonic-clonic (SGTC)		
Total	93	95
Decrease		
-100 to <-75	39 (41.9)	45 (47.4)
-75 to <-50	18 (19.4)	17 (17.9)
-50 to <-25	9 (9.7)	9 (9.5)
-25 to <0	8 (8.6)	8 (8.4)
Increase		
0 to <25	9 (9.7)	3 (3.2)
25 to <50	1 (1.1)	7 (7.4)
50 to <75	2 (2.2)	2 (2.1)
≥75	7 (7.5)	4 (4.2)

Table 7. Distribution of Percent Change From Baseline to Double Blind Phase in 28-Day Seizure Rate - FAS Population

Percent Change in 28-Day Seizure Rate	Pregabalin (N=253) n (%)	Levetiracetam (N=254) n (%)

Double blind phase for all partial seizures and simple partial seizure refers to titration and maintenance phases.
Double blind phase for complex partial seizure and SGTC refers to titration and maintenance phases.
Percentages were calculated using Total as denominator.
FAS = full analysis set; SGTC = secondarily generalized tonic-clonic; N = number of FAS subjects under each treatment group; n = number of subjects in the given group.

Proportion of SGTC/All Partial Seizures: Proportion of 28-day SGTC seizure rate to 28-day all partial seizure rate for SGTC population is summarized in Table 8. A mean increase was observed at the end of the double-blind phase (titration + maintenance), when compared to baseline (with mean [SD] of 3.9 [30.16] and 6.3 [32.07] in the pregabalin and levetiracetam groups, respectively). Considering the variability of the data, the changes are considered similar in both treatment groups.

Table 8. Summary of Proportion (28-Day SGTC Seizure Rate to 28-Day All Partial Seizure Rate) - SGTC Population

Phase	Pregabalin (N=107)	Levetiracetam (N=111)
Baseline		
n	107	111
Mean (SD)	39.4 (38.14)	38.9 (35.87)
Median	25	25
Range	0.0 - 100.0	0.0 - 100.0
Titration		
n	93	93
Mean (SD)	39.1 (43.37)	40.0 (42.04)
Median	17.07	20
Range	0.0 - 100.0	0.0 - 100.0
Change from baseline		
n	93	93
Mean (SD)	2.8 (32.84)	3.3 (32.32)
Median	0	0
Range	-100.0 - 100.0	-100.0 - 100.0
Maintenance		
n	89	85
Mean (SD)	40.2 (40.74)	40.6 (42.07)
Median	22.22	28
Range	0.0 - 100.0	0.0 - 100.0
Change from baseline		
n	89	85
Mean (SD)	4.9 (30.87)	7.6 (37.33)
Median	0	0
Range	-100.0 - 84.6	-95.8 - 100.0
Double-blind		
n	102	101
Mean (SD)	42.0 (40.39)	42.1 (39.64)
Median	28.42	33.33
Range	0.0 - 100.0	0.0 - 100.0
Change from baseline		
n	102	101
Mean (SD)	3.9 (30.16)	6.3 (32.07)
Median	0	0
Range	-100.0 - 84.6	-80.8 - 100.0

Double-blind phase refered to titration and maintenance phases.
Proportion of 28-Day SGTC seizure rate to 28-Day all partial seizure rate was expressed as a percentage.
N = number of SGTC subjects under each treatment group; n = number of subjects that could be analyzed;
SGTC = secondarily generalized tonic-clonic; SD = standard deviation.

SGTC Responder: There was no significant difference between treatment groups in SGTC responder rate (p=0.5724) as summarized in Table 9.

Table 9. Summary of SGTC Responders - Reduction in Proportion of 28-Day SGTC Seizure Rate to 28-Day All Partial Seizure Rate (Fisher's Exact Test)-SGTC Population

	Pregabalin (N=107)	Levetiracetam (N=111)	p-Value[a]
n	102	101	0.5724
Response (%)	42 (41.2)	46 (45.5)	
No Response (%)	60 (58.8)	55 (54.5)	
95% CI	(31.6, 50.7)	(35.8, 55.3)	

Double-blind phase refered to titration and maintenance phases.
SGTC Responder was defined as a subject who showed reduction from baseline to double-blind phase in proportion of 28-day SGTC seizure rate to 28-day all partial seizure rate.
Percentages were calculated in reference to n.
CI = confidence interval; N = number of SGTC subjects under each treatment group; n = number of subjects that can be analyzed; SGTC = secondarily generalized tonic-clonic.
a. p-value comes from the 2-sided Fisher's Exact Test.

Twenty eight-Day Seizure Rate: Twenty eight-day seizure rate is presented by phase for all partial seizures for the FAS and PP population in Table 10 and Table 11, respectively. Twenty eight-day seizure rate during all phases were similar in both treatment groups. At baseline, for the FAS population, the mean (SD) 28-day seizure rate was 17.4 (41.25) and 16.7 (29.82) for the pregabalin and levetiracetam groups, respectively. The mean (SD) 28-day seizure rate decreased to 14.7 (44.51) and 11.3 (33.69) for the pregabalin and levetiracetam groups, respectively at the end of the titration phase and further decreased to 11.0 (34.34) and 9.3 (26.44) for the pregabalin and levetiracetam groups, respectively at the end of the maintenance phase. Similar decreases in 28-day seizure rate were reported for the PP population.

Table 10. Summary of 28-Day Seizure Rate by Phase - All Partial Seizures - FAS Population

Phase	Pregabalin (N=253)	Levetiracetam (N=254)
Baseline		
n	253	254
Mean (SD)	17.4 (41.25)	16.7 (29.82)
Median	7.8	7.5
Range	2-574	1-237
Titration		
n	253	254
Mean (SD)	14.7 (44.51)	11.3 (33.69)
Median	4	3.6
Range	0-514	0-408
Maintenance		
n	226	236
Mean (SD)	11.0 (34.34)	9.3 (26.44)
Median	3.4	2.9
Range	0-366	0-308
Double-blind		
n	253	254
Mean (SD)	13.2 (35.22)	10.3 (28.36)
Median	4	3.5
Range	0-325	0-335

Double-blind phase refered to titration and maintenance phases.
FAS = full analysis set; N = the number of FAS subjects under each treatment group; n = number of subjects that could be analyzed; SD = standard deviation.

Table 11. Summary of 28-Day Seizure Rate by Type - FAS Population

Seizure Type	Baseline	Maintenance	Baseline	Maintenance
All partial seizure				
n	253	226	254	236
Mean (SD)	17.4 (41.25)	11.0 (34.34)	16.7 (29.82)	9.3 (26.44)
Median	7.8	3.4	7.5	2.9
Range	2-574	0-366	1-237	0-308
Simple partial				
n	253	226	254	236
Mean (SD)	8.2 (39.87)	6.2 (28.20)	6.9 (18.76)	4.2 (16.60)
Median	0	0	0	0
Range	0-574	0-261	0-223	0-169
Complex partial				
n	253	226	254	236
Mean (SD)	7.1 (10.78)	3.7 (10.88)	8.2 (22.28)	4.5 (14.74)
Median	3.9	1	3.3	0.3
Range	0-74	0-111	0-237	0-150
Secondarily generalized tonic-clonic				
n	253	226	254	236
Mean (SD)	2.1 (8.16)	1.1 (7.39)	1.7 (3.92)	0.6 (1.63)
Median	0	0	0	0
Range	0-107	0-108	0-33	0-13

FAS = full analysis set; N = number of FAS subjects under each treatment group; n = number of subjects that could be analyzed; SD = standard deviation.

Seizure Free Rate: Summary of seizure free for last 28 days of maintenance phase is summarized in Table 12. Overall, 40 (19.9%) and 58 (27.6%) subjects in the pregabalin and levetiracetam groups, respectively showed seizure free response for all partial seizures for at least 28 consecutive days from their last seizure until the end of maintenance phase. There was no significant difference between treatments in seizure free rate for all partial seizures (p=0.0822), simple partial seizures (p=0.9175) and SGTC seizures (p=0.7139). However, more subjects were considered seizure free for complex partial seizures in the levetiracetam group compared to the pregabalin group (59.0% and 49.3% respectively; p=0.0483). Subjects counted in this category could have experienced other types of seizures during the study.

Table 12. Summary of Seizure Free for Last 28 Days of Maintenance Phase (Fisher's Exact Test) - FAS Population

Seizure Type	Pregabalin (N=253)	Levetiracetam (N=254)	p-Value[a]
All partial seizure			
n	201	210	0.0822
Response (%)	40 (19.9)	58 (27.6)	
No response (%)	161 (80.1)	152 (72.4)	
95% CI	(14.4, 25.4)	(21.6, 33.7)	
Simple partial			
n	201	210	0.9175
Response (%)	132 (65.7)	139 (66.2)	
No Response (%)	69 (34.3)	71 (33.8)	
95% CI	(59.1, 72.2)	(59.8, 72.6)	
Complex partial			
n	201	210	0.0483
Response (%)	99 (49.3)	124 (59.0)	
No Response (%)	102 (50.7)	86 (41.0)	
95% CI	(42.3, 56.2)	(52.4, 65.7)	
Secondarily generalized tonic-clonic			
n	201	210	0.7139
Response (%)	162 (80.6)	166 (79.0)	
No Response (%)	39 (19.4)	44 (21.0)	
95% CI	(75.1, 86.1)	(73.5, 84.6)	

Subjects were seizure free when they did not have any seizure for at least 28 consecutive days from their last seizure until the end of the maintenance phase. Subject can be seizure free for a specific type of seizure but not necessarily for the other types.
Percentages were calculated in reference to n.
CI = confidence interval; FAS = full analysis set; N = number of FAS subjects under each treatment group; n = number of subjects having non-missing diaries during 28 days before the end of maintenance phase.
a. p-Value comes from the 2-sided Fisher's Exact Test.

Brief Psychiatric Rating Scale (BPRS): BPRS-A total and core scores (psychosis cluster) are presented in Table 13 and Table 14, respectively. BPRS-A total score ranges from 18 to 126 and higher scores indicate more impairment. At baseline, the mean (SD) BPRS-A total scores were similar for both treatment groups (27.07 [9.58] and 25.72 [9.53] in the pregabalin and levetiracetam groups, respectively). The total scores ranged from 18 to 65 and 18 to 68, in the pregabalin and levetiracetam groups, respectively. An improvement was observed in the total scores at Week 16. However, the improvement was not statistically significant. The

mean (SD) changes in BPRS-A scores from baseline at Week 16/early termination (ET) were -3.06 (7.16) and -1.73 (7.58) in the pregabalin and levetiracetam groups, respectively with no statistically significant difference between groups.

Table 13. Brief Psychiatric Rating Scale (BPRS) Total BPRS Score: Results of Analysis of Covariance - FAS Population

	Treatment	N	n	Min	Med	Max	Mean (SD)	LS Mean (SE)	Difference (SE)	95% CI	p-Value
Baseline	Pregabalin	253	253	18.00	24.00	65.00	27.07 (9.58)	27.26 (0.55)	1.17 (0.78)	(-0.36, 2.69)	0.1334
	Levetiracetam	254	254	18.00	22.00	68.00	25.72 (9.53)	26.09 (0.56)			
Change from Baseline to Week 7	Pregabalin	253	217	-36.00	-1.00	17.00	-2.62 (6.07)	-2.16 (0.36)	-0.46 (0.50)	(-1.45, 0.53)	0.3638
	Levetiracetam	254	225	-35.00	0.00	24.00	-1.53 (6.78)	-1.70 (0.36)			
Change from Baseline to Week 10	Pregabalin	253	217	-37.00	-1.00	29.00	-3.07 (7.15)	-2.64 (0.37)	-0.23 (0.53)	(-1.26, 0.81)	0.6640
	Levetiracetam	254	219	-35.00	-1.00	24.00	-2.21 (7.01)	-2.42 (0.38)			
Change from Baseline to Week 13	Pregabalin	253	209	-39.00	-2.00	15.00	-3.35 (7.02)	-2.99 (0.39)	-0.31 (0.55)	(-1.38, 0.76)	0.5701
	Levetiracetam	254	214	-36.00	-1.00	27.00	-2.58 (7.90)	-2.68 (0.39)			
Change from Baseline to Week 16/ET	Pregabalin	253	235	-45.00	-2.00	26.00	-3.06 (7.16)	-2.70 (0.40)	-0.77 (0.56)	(-1.88, 0.33)	0.1697
	Levetiracetam	254	241	-29.00	-1.00	29.00	-1.73 (7.58)	-1.92 (0.40)			
Change from Baseline to Followup	Pregabalin	253	178	-41.00	-1.00	25.00	-3.34 (7.63)	-2.77 (0.44)	-1.35 (0.61)	(-2.54, -0.16)	0.0262
	Levetiracetam	254	189	-25.00	-1.00	32.00	-1.63 (7.41)	-1.42 (0.43)			

Total BPRS score ranges from 18 to 126 and higher score indicates more impairment.
LS Means from the ANCOVA Model with main effects of treatment and combined center. For post-baseline assessments baseline was included as a covariate.
Treatment difference was (Pregabalin-Levetiracetam) in LS mean
ANCOVA = analysis of covariance; BPRS = Brief Psychiatric Rating Scale; CI = confidence interval; ET = early termination; FAS = full analysis set; LS = Least Squares; max=maximum; med=median; min=minimum; N = number of FAS subjects under each treatment group; n = number of subjects that could be analyzed for the week; SD = standard deviation, SE = standard error.

Table 14. Brief Psychiatric Rating Scale (BPRS) Core BPRS Score: Results of Analysis of Covariance - FAS Population

	Treatment	N	n	Min	Med	Max	Mean (SD)	LS Mean (SE)	Difference (SE)	95% CI	p-Value
Baseline	Pregabalin	253	253	4	4	18	5.14 (2.29)	5.18 (0.13)	0.17 (0.18)	(-0.19, 0.52)	0.3551
	Levetiracetam	254	254	4	4	16	4.94 (1.85)	5.01 (0.13)			
Change from Baseline to Week 7	Pregabalin	253	216	-14	0	2	-0.41 (1.47)	-0.34 (0.08)	-0.12 (0.11)	(-0.34, 0.09)	0.2457
	Levetiracetam	254	225	-9	0	4	-0.23 (1.43)	-0.22 (0.08)			
Change from Baseline to Week 10	Pregabalin	253	217	-14	0	5	-0.48 (1.96)	-0.40 (0.08)	-0.06 (0.12)	(-0.30, 0.17)	0.595
	Levetiracetam	254	219	-9	0	3	-0.34 (1.47)	-0.34 (0.08)			
Change from Baseline to Week 13	Pregabalin	253	209	-14	0	4	-0.59 (1.91)	-0.51 (0.07)	-0.12 (0.10)	(-0.33, 0.08)	0.2452
	Levetiracetam	254	214	-8	0	5	-0.40 (1.56)	-0.38 (0.07)			
Change from Baseline to Week 16/ET	Pregabalin	253	235	-14	0	4	-0.46 (1.81)	-0.40 (0.08)	-0.14 (0.11)	(-0.36, 0.09)	0.2283
	Levetiracetam	254	241	-8	0	6	-0.26 (1.58)	-0.26 (0.08)			
Change from Baseline to Follow-up	Pregabalin	253	178	-14	0	4	-0.48 (1.67)	-0.37 (0.10)	-0.26 (0.13)	(-0.52, 0.00)	0.0495
	Levetiracetam	254	189	-5	0	10	-0.17 (1.60)	-0.11 (0.10)			

Core BPRS score ranges from 4 to 28 and higher score indicates more impairment.
LS Means from the ANCOVA Model with main effects of treatment and combined center. For post-baseline assessments baseline was included as a covariate.
Treatment difference was (Pregabalin-Levetiracetam) in LS mean.
ANCOVA = analysis of covariance; BPRS = Brief Psychiatric Rating Scale; CI = confidence interval; ET = early termination; FAS = full analysis set; LS = Least Squares; max=maximum; med=median; min=minimum; N = number of FAS subjects under each treatment group; n = number of subjects that could be analyzed for the week; SD=standard deviation, SE = standard error.

Hospital Anxiety and Depression Scale (HADS): HADS anxiety score ranges from 0 to 21 and higher scores indicates more anxiety. Changes from baseline and distribution by severity level are summarized in Table 15 and Table 16, respectively for anxiety subscale total score. HADS anxiety score ranges from 0 to 21 and higher scores indicates more anxiety. HADS scores at baseline indicate that the population had levels of anxiety which were approximately within the normal range (score 0-7). The mean (SD; range) scores at baseline were 7.32 (4.19; 0 to 19) and 7.22 (4.03; 0 to 20) in the pregabalin and levetiracetam groups, respectively. An improvement was observed in the total scores at Week 16. However, the improvement was not statistically significant. There was a decrease in total scores at Week 16/ET visit with mean (SD) scores of 6.21 (4.01) and 6.01 (3.69), and mean changes from baseline of -1.01 (3.66) and -1.18 (3.82) in the pregabalin and levetiracetam groups, respectively. No statistically significant difference was observed between the groups.

HADS depression score ranges from 0 to 21 and higher scores indicates more depression. Changes from baseline and distribution by severity level are summarized in Table 17 and Table 18, respectively for depression subscale total score. HADS depression score ranges from 0 to 21 and higher scores indicates more depression. HADS depression scores at baseline indicate that the population had levels of depression which fell within the normal range (score 0-7). The mean (SD; range) scores at baseline were 6.23 (4.14; 0 to 18) and 5.72 (4.02; 0 to 19) in the pregabalin and levetiracetam groups, respectively. An improvement was observed in the total scores at Week 16. However, the improvement was not statistically significant. There was a decrease in total scores at Week 16/ET visit with mean (SD) scores of 5.50 (4.02) and 5.23 (4.06), and mean changes from baseline of -0.59 (3.91) and -0.42 (3.19) in the pregabalin and levetiracetam groups, respectively. No statistically significant difference was observed between the groups.

Table 15. Hospital Anxiety and Depression Scale Anxiety Subscale Total Score Change From Baseline: Results of Analysis of Covariance - FAS Population

	Treatment	N	n	Min	Med	Max	Mean (SD)	LS Mean (SE)	Difference (SE)	95% CI	p-Value
Baseline	Pregabalin	253	253	0	7	19	7.32 (4.19)	7.25 (0.26)	-0.09 (0.37)	(-0.82, 0.64)	0.8084
	Levetiracetam	254	253	0	7	20	7.22 (4.03)	7.34 (0.27)			
Week 16/ET	Pregabalin	253	228	0	6	18	6.21 (4.01)	6.32 (0.22)	0.25 (0.30)	(-0.34, 0.85)	0.4008
	Levetiracetam	254	241	0	6	19	6.01 (3.69)	6.06 (0.22)			
Change from Baseline to Week 16/ET	Pregabalin	253	228	-11	-1	10	-1.01 (3.66)	-0.89 (0.22)	0.25 (0.30)	(-0.34, 0.85)	0.4008
	Levetiracetam	254	240	-14	-1	10	-1.18 (3.82)	-1.15 (0.22)			

Anxiety score ranges from 0 to 21 and higher score indicates more anxiety.
LS Means from the ANCOVA Model with main effects of treatment and combined center. For post-baseline assessments baseline was included as a covariate.
Treatment difference was (Pregabalin-Levetiracetam) in LS mean.
ANCOVA = analysis of covariance; CI = confidence interval; ET = early termination; FAS = full analysis set; LS = least squares; N = number of FAS subjects under each treatment group; n = number of subjects that could be analyzed for the week; SD = standard deviation, SE = standard error.

Table 16. Hospital Anxiety and Depression Scale (HADS) - Distribution of Anxiety Subscale Total Score Severity Level by Visit by Treatment Group - FAS Population

	Pregabalin (N=253)				
	Baseline				
Week 16/Early Termination	Normal n (%)	Mild n (%)	Moderate n (%)	Severe n (%)	Total n (%)
Normal	102 (40.3)	28 (11.1)	16 (6.3)	2 (0.8)	148 (58.5)
Mild	16 (6.3)	18 (7.1)	11 (4.3)	1 (0.4)	46 (18.2)
Moderate	6 (2.4)	6 (2.4)	11 (4.3)	4 (1.6)	27 (10.7)
Severe	1 (0.4)	0	4 (1.6)	2 (0.8)	7 (2.8)
Total	125 (49.4)	52 (20.6)	42 (16.6)	9 (3.6)	228 (90.1)

Severity: Normal (0-7), Mild (8-10), Moderate (11-14), Severe (15-21).
Only subjects having baseline and Week 16/Early Termination measurement were analyzed.
Percentages were calculated in reference to N.
N = number of FAS subjects under each treatment group; n = number of subjects that could be analyzed; FAS = full analysis set; SD = standard deviation.

Table 17. Hospital Anxiety and Depression Scale (HADS) Depression Subscale Total Score Change From Baseline: Results of Analysis of Covariance - FAS Population

	Treatment	N	n	Min	Med	Max	Mean (SD)	LS Mean (SE)	Difference (SE)	95% CI	p-Value
Baseline	Pregabalin	253	253	0	6	18	6.23 (4.14)	6.22 (0.25)	0.22 (0.35)	(-0.47, 0.91)	0.5263
	Levetiracetam	254	253	0	5	19	5.72 (4.02)	6.00 (0.25)			
Week 16/ET	Pregabalin	253	228	0	5	18	5.50 (4.02)	5.41 (0.22)	-0.01 (0.30)	(-0.61, 0.59)	0.9749
	Levetiracetam	254	241	0	4	19	5.23 (4.06)	5.42 (0.22)			
Change from Baseline to Week 16/ET	Pregabalin	253	228	-10	-1	13	-0.59 (3.91)	-0.46 (0.22)	-0.01 (0.30)	(-0.61, 0.59)	0.9749
	Levetiracetam	254	240	-10	0	10	-0.42 (3.19)	-0.45 (0.22)			

Depression score ranges from 0 to 21 and higher score indicates more depression.
LS Means from the ANCOVA Model with main effects of treatment and combined center. For post-baseline assessments baseline was included as a covariate.
Treatment difference was (Pregabalin-Levetiracetam) in LS mean..
ANCOVA = analysis of covariance; CI = confidence interval; ET = early termination; FAS = full analysis set; LS = least squares; N = number of FAS subjects under each treatment group; n = number of subjects that could be analyzed for the week; SD = standard deviation, SE = standard error.

Table 18. Hospital Anxiety and Depression Scale (HADS) - Distribution of Depression Subscale Total Score Severity Level by Visit by Treatment Group - FAS Population

	Pregabalin (N=253)				
	Baseline				
Week 16/Early	Normal n (%)	Mild n (%)	Moderate n (%)	Severe n (%)	Total n (%)
Normal	122 (48.2)	31 (12.3)	9 (3.6)	0	162 (64.0)
Mild	12 (4.7)	14 (5.5)	12 (4.7)	1 (0.4)	39 (15.4)
Moderate	11 (4.3)	5 (2.0)	7 (2.8)	1 (0.4)	24 (9.5)
Severe	0	1 (0.4)	1 (0.4)	1 (0.4)	3 (1.2)
Total	145 (57.3)	51 (20.2)	29 (11.5)	3 (1.2)	228 (90.1)

Severity: Normal (0-7), Mild (8-10), Moderate (11-14), Severe (15-21).
Only subjects having baseline and Week 16/Early Termination measurement were analyzed.
Percentages were calculated in reference to N.
N = number of FAS subjects under each treatment group; n = number of subjects that could be analyzed; FAS = full analysis set; SD = standard deviation.

MOS-Sleep Scale: The MOS-SS yields 7 subscales (sleep disturbance, snoring, awakening short of breath or with a headache, quantity of sleep, optimal sleep, sleep adequacy, and somnolence) and a 9 item overall sleep problems index was also calculated. The quantity of sleep subscale score ranges from 0 to 24, indicating the number of hours of sleep. The optimal sleep score is a dichotomous 'Yes' or 'No' rating, where 'Yes' indicates optimal sleep (average 7-8 hours per night) and 'No' indicates not optimal sleep. The remaining subscales (sleep disturbance, snoring, awaken short of breath, adequacy of sleep and somnolence) and the overall sleep problems index produce scores that range from 0 to 100. Higher scores indicate greater impairment/more of a problem (negative changes thereby indicate improvement) for all except the adequacy of sleep subscale where a higher score indicates less impairment/more adequate sleep (positive changes thereby indicate improvement).

There were no significant changes in MOS-SS at Week 16/ET from baseline except for snoring where mean (SD) changes from baseline were 2.87 (27.73) and -7.58 (29.91) for the pregabalin and levetiracetam groups, respectively. The difference between the treatment groups was statistically significant ($p<0.0001$) in favor of levetiracetam.

Mean (SD) changes from baseline in the MOS sleep subscale scores are presented in Table 19.

Table 19. Change From Baseline to Week 16/ET in MOS Sleep Subscale Scores (FAS Population)

	Pregabalin (N=253)		Levetiracetam (N=254)	
MOS Sleep Subscale	**n**	**Mean (SD) Change From Baseline to Week 16/ET**	**n**	**Mean (SD) Change From Baseline to Week 16/ET**
Sleep disturbance	230	-5.86 (20.65)	240	-4.50 (21.86)
Snoring	230	2.87 (27.73)	240	-7.58 (29.91)
Awaken short of breath	230	-1.22 (24.91)	241	-2.99 (27.47)
Quantity of sleep	230	0.16 (1.54)	239	0.03 (1.51)
Adequacy of sleep	230	0.00 (29.61)	241	1.78 (29.11)
Somnolence	230	-2.99 (24.80)	241	-0.11 (23.81)
Sleep problem index (9)	230	-3.19 (16.41)	240	-3.21 (17.22)

ET = early termination; FAS = full analysis set; MOS = medical outcome of sleep; N = number of FAS subjects under each treatment group; n = number of subjects that could be analyzed for the week; SD = standard deviation.

Safety Results:

All causalities TEAEs reported during the entire study (includes double-blind titration and maintenance phases, blinded continuation phase, and follow-up phase) are summarized in Table 20. Overall, 380 subjects (200 [78.7%] and 180 [70.6%] subjects in the pregabalin and levetiracetam groups, respectively) experienced at least 1 TEAE. Of these, 24 subjects in each pregabalin and levetiracetam groups reported SAEs, 23 (9.1%) and 22 (8.6%) subjects in the pregabalin and levetiracetam groups, respectively reported severe AEs.

Table 20. Treatment-Emergent Adverse Events (All Causalities)

Number (%) of Subjects	Pregabalin	Levetiracetam
Subjects evaluable for adverse events	254	255
Number of adverse events	740	636
Subjects with adverse events	200 (78.7)	180 (70.6)
Subjects with serious adverse events	24 (9.4)	24 (9.4)
Subjects with severe adverse events	23 (9.1)	22 (8.6)
Subjects discontinued due to adverse events	28 (11.0)	21 (8.2)
Subjects with dose reduced or temporary discontinuation due to adverse events	21 (8.3)	12 (4.7)

Includes data up to 999 days after last dose of study drug.
Except for the number of adverse events subjects were counted only once per treatment in each row.
Serious adverse events - according to the investigator's assessment.
Discontinued due to adverse events - only subjects having discontinuation due to adverse events indicated on subject summary pages were summarized.
MedDRA (version 15.1) coding dictionary applied.
MedDRA = Medical Dictionary for Regulatory Activities.

Treatment-emergent non SAEs by system organ class and preferred term (all causalities) for events reported for ≥5% subjects are summarized in Table 21. The largest proportion of subjects in both treatment groups (125 [49.2%] and 112 [43.9%] subjects in the pregabalin and levetiracetam groups, respectively) reported TEAEs from the nervous system disorders SOC. The most frequently reported TEAEs in both treatment groups were somnolence (reported by 83 [32.7%] and 76 [29.8%] subjects in the pregabalin and levetiracetam groups, respectively) and dizziness (reported by 59 [23.2%] and 42 [16.5%] subjects in the pregabalin and levetiracetam groups, respectively). The majority of all causalities TEAEs were mild or moderate in severity.

Table 21. Treatment-Emergent Non-Serious Adverse Events by System Organ Class and Preferred Term (All Causalities) for Events Having a Frequency Rate ≥5

System Organ Class Preferred Term	Pregabalin (N=254) n (%)	Levetiracetam (N=255) n (%)
Gastrointestinal disorders	5 (2.0)	15 (5.9)
Nausea	5 (2.0)	15 (5.9)
Infections and infestations	24 (9.4)	19 (7.5)
Nasopharyngitis	24 (9.4)	19 (7.5)
Investigations	26 (10.2)	8 (3.1)
Weight increased	26 (10.2)	8 (3.1)
Nervous system disorders	125 (49.2)	112 (43.9)
Dizziness	59 (23.2)	42 (16.5)
Headache	37 (14.6)	30 (11.8)
Somnolence	83 (32.7)	76 (29.8)
Psychiatric disorders	5 (2.0)	15 (5.9)
Insomnia	5 (2.0)	15 (5.9)
Total preferred term events	148 (58.3)	127 (49.8)

Subjects were only counted once per treatment for each row.
Included data up to 999 days after last dose of study drug.
MedDRA (version 15.1) coding dictionary applied.
MedDRA = Medical Dictionary for Regulatory Activities; N = total number of subjects in a treatment group; n=number of subjects in a given reporting criteria.

Considering only discontinuations due to AEs with onset after the start of study treatment, 28 (11.0%) and 21 (8.2%) subjects in the pregabalin and levetiracetam groups, respectively permanently discontinued study treatment due to TEAEs. During the double-blind titration and maintenance phases, 16 (6.3%) and 14 (5.5%) subjects in the pregabalin and levetiracetam groups, respectively discontinued study treatment due to TEAEs. Of the subjects who entered the blinded continuation phase, 11 (5.9%) and 7 (3.6%) subjects in the pregabalin and levetiracetam groups, respectively discontinued study treatment due to TEAEs.

Considering only discontinuations due to AEs with onset after the start of study treatment, 21 (8.3%) and 12 (4.7%) subjects in the pregabalin and levetiracetam groups, respectively temporarily discontinued study treatment or had dose reduced due to TEAEs. During the double-blind titration and maintenance phases, 21 (8.3%) and 10 (3.9%) subjects in the pregabalin and levetiracetam groups, respectively temporarily discontinued study treatment or had their dose reduced due to TEAEs. Of the subjects who entered the blinded continuation phase, 14 (7.6%) and 6 (3.1%) subjects in the pregabalin and levetiracetam groups, respectively temporarily discontinued study treatment or had their dose reduced due to TEAEs. Dose reduction of study treatment was not permitted by the protocol during the blinded continuation phase and those subjects who did reduce their dose during this phase were considered as protocol deviations.

In total, 24 subjects in each pregabalin and levetiracetam groups reported treatment-emergent SAEs during the study (Table 22). The majority were considered unrelated to study treatment by the investigator. Overall, 4 SAEs reported by 3 subjects in the pregabalin

group, and 11 SAEs reported by 7 subjects in the levetiracetam were considered related to study treatment by the Investigator.

Overall 5 subjects (2 and 3 subjects in the pregabalin and levetiracetam groups, respectively) died during the study (Table 23). Of these, 2 deaths in the levetiracetam group occurred >30 days after therapy stop date. None of the deaths were considered related to study treatment by the investigator. One subject died during the pre-randomization period.

Table 24 and Table 25 present the permanent discontinuations due to TEAEs.

Table 22. Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term (All Causalities)

Serious Adverse Events Preferred Term	Pregabalin (N=254)	Levetiracetam (N=255)
	n (%)	n (%)
Number (%) of subjects with adverse events	24 (9.4)	24 (9.4)
Blood and lymphatic system disorders	1 (0.4)	1 (0.4)
Neutropenia	1 (0.4)	0
Thrombocytopenia	0	1 (0.4)
Gastrointestinal disorders	1 (0.4)	1 (0.4)
Gastroduodenitis	1 (0.4)	0
Haemorrhoids	0	1 (0.4)
General disorders and administration site conditions	2 (0.8)	1 (0.4)
Asthenia	1 (0.4)	0
Drowning	1 (0.4)	0
Polyp	0	1 (0.4)
Infections and infestations	4 (1.6)	4 (1.6)
Abscess limb	1 (0.4)	0
Acute tonsillitis	0	1 (0.4)
Bronchitis	1 (0.4)	0
Bronchopneumonia	1 (0.4)	0
Pharyngotonsillitis	0	1 (0.4)
Pneumonia	0	1 (0.4)
Pulmonary tuberculosis	0	1 (0.4)
Septic shock	1 (0.4)	0
Urinary tract infection	1 (0.4)	0
Injury, poisoning and procedural complications	6 (2.4)	4 (1.6)
Brain contusion	0	1 (0.4)
Burns third degree	1 (0.4)	0
Clavicle fracture	0	1 (0.4)
Craniocerebral injury	1 (0.4)	0
Fall	1 (0.4)	1 (0.4)
Hip fracture	1 (0.4)	0
Humerus fracture	1 (0.4)	0
Intentional overdose	0	1 (0.4)
Laceration	1 (0.4)	0
Spinal compression fracture	0	1 (0.4)
Subdural haematoma	1 (0.4)	0
Thermal burn	1 (0.4)	0
Wrist fracture	1 (0.4)	0
Investigations	2 (0.8)	0
Weight increased	2 (0.8)	0
Metabolism and nutrition disorders	0	1 (0.4)
Hyponatraemia	0	1 (0.4)
Musculoskeletal and connective tissue disorders	2 (0.8)	1 (0.4)
Costochondritis	1 (0.4)	0
Rotator cuff syndrome	1 (0.4)	0
Spinal disorder	0	1 (0.4)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	0	1 (0.4)
Retroperitoneal cancer	0	1 (0.4)

Table 22. Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term (All Causalities)

Serious Adverse Events Preferred Term	Pregabalin (N=254) n (%)	Levetiracetam (N=255) n (%)
Nervous system disorders	7 (2.8)	10 (3.9)
Complex partial seizures	0	1 (0.4)
Convulsion	5 (2.0)	1 (0.4)
Dizziness	1 (0.4)	0
Drug withdrawal convulsions	0	1 (0.4)
Epilepsy	1 (0.4)	2 (0.8)
Ischaemic stroke	0	1 (0.4)
Postictal state	0	1 (0.4)
Sedation	0	1 (0.4)
Status epilepticus	1 (0.4)	2 (0.8)
Pregnancy, puerperium and perinatal conditions	1 (0.4)	1 (0.4)
Abortion spontaneous	1 (0.4)	0
Abortion threatened	0	1 (0.4)
Psychiatric disorders	2 (0.8)	6 (2.4)
Aggression	0	2 (0.8)
Depressed mood	0	1 (0.4)
Personality change	0	1 (0.4)
Personality disorder	1 (0.4)	0
Somatoform disorder neurologic	1 (0.4)	0
Suicide attempt	0	2 (0.8)
Reproductive system and breast disorders	1 (0.4)	1 (0.4)
Benign prostatic hyperplasia	0	1 (0.4)
Ovarian cyst	1 (0.4)	0
Vascular disorders	0	1 (0.4)
Deep vein thrombosis	0	1 (0.4)

Subjects were only counted once per treatment for each row.
Included data up to 999 days after last dose of study drug.
MedDRA (version 15.1) coding dictionary applied.
MedDRA = Medical Dictionary for Regulatory Activities; N = total number of subjects in a treatment group; n=number of subjects in a given reporting criteria.

Table 23. Deaths

Serial Number	Treatment Group/Dose	Suspect Drug /Dose[a]	Action Taken (Drug Level)	Therapy Stop Date	Day of Death[b]	Date of Death	Event With Fatal Outcome-Preferred Term	Cause of Death-Preferred Term
1.	Pre-randomization	Erythromycin[c]	N/A	N/A	N/A	03-Sep-2010	Sepsis	Drug hypersensitivity/Pneumonia aspiration/Sepsis
2.	Pregabalin/ 300 mg	Pregabalin/ 300 mg	Permanently withdrawn	25-Nov-2008	115	25-Nov-2008	Drowning	Drowning
3.	Pregabalin/ 300 mg	Pregabalin/ 300 mg	Permanently withdrawn	26-Jul-2009	240	19-Aug-2009	Bronchopneumonia Septic shock Subdural haemorrhage	Pneumonia/Septic shock Pneumonia/Septic shock Pneumonia / Septic shock
4.	Levetiracetam/ 1000 mg	Levetiracetam	Permanently withdrawn	04-Apr-2009	491	22-Sep-2009	Retroperitoneal cancer	Retroperitoneal cancer
5.	Levetiracetam/ 2000 mg	Levetiracetam	Permanently withdrawn	29-Jul-2009	165	12-Sep-2009	Foetal exposure during pregnancy[d] Premature baby[e]	Premature baby Premature baby
6.	Levetiracetam/ 2000 mg	Levetiracetam /1000 mg	Permanently withdrawn	12-Nov-2010	151	21-Nov-2010	Status epilepticus	Death

MedDRA version 15.1 coding dictionary applied.
MedDRA = Medical Dictionary For Regulatory Activities; N/A = not applicable; OC = oracle clinical; PIMS = Phase I Management System; SDW = safety data warehouse.

a. Source of actual treatment group or sequence is OC or PIMS. Source of suspect drug is from SDW.
b. Day of death was calculated as SDW death date minus OC first active therapy + plus 1.
c. Erythromycin was discontinued on 13 August 2010.
d. The local laboratory reports from the site showed that the subject's pregnancy tests were negative through Week 7 on study drug (Day 51, 21 May 2009). On Day 114 (23 July 2009), the pregnancy test was first positive and the subject was discontinued on 29 July 2009. However, the CIOMS report stated that the neonate appeared 22 weeks when born prematurely on 31 July 2009.
e. Preterm neonate died 5 minutes after delivery.

Table 24. Permanent Discontinuations Due to Treatment-Emergent Adverse Events at Double-Blind Titration+Maintenance Phases

Serial Number	MedDRA Preferred Term	Treatment at Onset	Study Start Day[a]/Stop Day[a]	Severity/Outcome	Causality	SAE (Yes/No)
1	Dizziness	Pregabalin	4/8	Moderate/resolved	Study drug	No
2	Chest pain	Pregabalin	2/3	Mild/resolved	Study drug	No
	Dizziness	Pregabalin	2/3	Mild/resolved	Study drug	No
3	Convulsion[b]	Pregabalin	7/10	Moderate/resolved	Study drug	Yes
4	Increased appetite	Pregabalin	55/82	Mild/resolved	Study drug	No
5	Vertigo	Pregabalin	1/6	Severe/resolved	Study drug	No
6	Personality disorder	Pregabalin	72/77	Moderate/resolved	Disease under study	Yes
7	Headache	Pregabalin	8/[>55]	Moderate/still present	Study drug	No
8	Asthenia	Pregabalin	2/7	Severe/resolved	Study drug	No
9	Dizziness	Pregabalin	1/20	Mild/resolved	Study drug	No
10	Convulsion[c]	Pregabalin	10/11	Severe/resolved	Concomitant treatment	Yes
11	Somnolence	Pregabalin	12/12	Moderate/resolved	Study drug	No
12	Somnolence	Pregabalin	8/58	Mild/resolved	Study drug	No
13	Somnolence	Pregabalin	1/9	Moderate/resolved	Study drug	No
14	Hypersomnia	Pregabalin	1/22	Moderate/resolved	Study drug	No
15	Somnolence	Pregabalin	9/392	Mild/resolved	Study drug	No
16	Dizziness	Pregabalin	8/17	Moderate/resolved	Study drug	No
17	Dizziness	Levetiracetam	1/7	Moderate/resolved	Study drug	No
18	Dizziness	Levetiracetam	1/3	Severe/resolved	Study drug	No
19	Aggression	Levetiracetam	52/53	Severe/resolved	Study drug	Yes
20	Somnolence	Levetiracetam	1/[>30]	Mild/still present	Study drug	No
21	Dizziness	Levetiracetam	1/14	Moderate/resolved	Study drug	No
22	Acute psychosis	Levetiracetam	59/83	Moderate/resolved	Study drug	No
23	Rash pruritic	Levetiracetam	11/21	Moderate/resolved	Study drug	No
24	Rash	Levetiracetam	42/[>55]	Mild/still present	Study drug	No
25	Convulsion[d]	Levetiracetam	8/20	Mild/resolved	Study drug	No
26	Intentional overdose	Levetiracetam	24/24	Severe/resolved	Other-suicide attempt	Yes
	Sedation	Levetiracetam	24/25	Severe/resolved	Study drug	Yes
27	Dizziness	Levetiracetam	15/28	Mild/resolved	Study drug	No
	Depressed mood	Levetiracetam	15/28	Mild/resolved	Study drug	No
	Hypotension	Levetiracetam	15/28	Mild/resolved	Study drug	No
28	Fear	Levetiracetam	66/79	Moderate/resolved	Study drug	No
29	Dizziness	Levetiracetam	1/54	Mild/resolved	Study drug	No
30	Somnolence	Levetiracetam	51/105	Mild/resolved	Study drug	No

Table 24. Permanent Discontinuations Due to Treatment-Emergent Adverse Events at Double-Blind Titration+Maintenance Phases

Serial Number	MedDRA Preferred Term	Treatment at Onset	Study Start Day[a]/Stop Day[a]	Severity/Outcome	Causality	SAE (Yes/No)

[] Values in brackets are imputed from incomplete dates and times.
Only subjects having discontinuation due to adverse events indicated on subject summary pages are listed.
MedDRA (version 15.1) coding dictionary applied.
SAE according to Investigator's assessment.
MedDRA = Medical Dictionary for Regulatory Activities; SAE = serious adverse event.
a. Day relative to start of study treatment. First day of study treatment = Day 1.
b. The investigator reported term was increased frequency of seizures.
c. The investigator reported term was seizures not controlled.
d. The investigator reported term was seizure frequency increased.

Table 25. Permanent Discontinuations Due to Treatment-Emergent Adverse Events for Subjects Who Entered Blinded Continuation Phase

Serial Number	MedDRA Preferred Term	Treatment at Onset	Study Start Day[a]/Stop Day[a]	Severity/ Outcome	Causality	SAE (Yes/No)
1	Foetal exposure during pregnancy	Pregabalin	547/[928]	Severe/ resolved	Other-damaged condom	No
2	Dizziness	Pregabalin	369/[>371]	Mild/still present	Concomitant treatment	No
3	Tremor	Pregabalin	500/[>511]	Moderate/ still present	Study drug	No
4	Dizziness	Pregabalin	433/447	Moderate/ resolved	Concomitant treatment	No
5	Cranio-cerebral injury	Pregabalin	279/294	Moderate/ resolved	Other-subject had seizures, falls from height causing his own cranium trauma	Yes
6	Fall	Pregabalin	216/240	Severe/ resolved	Disease under study	Yes
7	Balance disorder	Pregabalin	4/207	Moderate/ resolved	Study drug	No
8	Weight increased	Pregabalin	469/[>545]	Moderate/ still present	Study drug	No
9	Maternal exposure timing unspecified	Pregabalin	117/121	Severe/ resolved	Disease under study	No
10	Hostility	Pregabalin	270/270	Mild/ resolved	Study drug	No
11	Weight increased	Pregabalin	8/177	Moderate/ resolved	Study drug	No
12	Depressed mood	Levetiracetam	312/388	Severe/ resolved	Study drug	Yes
13	Delusion	Levetiracetam	[687]/[>750]	Moderate/ still present	Study drug	No
14	Somnolence	Levetiracetam	[82]/[262]	Mild /resolved	Study drug	No
15	Depression	Levetiracetam	[52]/[171]	Moderate/ resolved	Study drug	No
16	Drug withdrawal convulsions	Levetiracetam	213/222	Moderate/ resolved	Other illness independent episode, not related to study drug, unknown	Yes
17	Convulsion	Levetiracetam	869/870	Severe/ resolved	Disease under study	Yes
18	Personality change	Levetiracetam	375/441	Moderate/ resolved	Other illness	Yes

Table 25. Permanent Discontinuations Due to Treatment-Emergent Adverse Events for Subjects Who Entered Blinded Continuation Phase

Serial Number	MedDRA Preferred Term	Treatment at Onset	Study Start Day[a]/Stop Day[a]	Severity/ Outcome	Causality	SAE (Yes/No)

Note: Data presentations for 'subjects who entered the blinded continuation phase' include a subset of subjects who entered the continuation phase but present data reported throughout the study ie, includes data from double blind titration and maintenance phases and blinded continuation phase.
[] Values in brackets were imputed from incomplete dates and times.
Only subjects discontinued due to adverse events indicated on subject summary pages.
MedDRA (version 15.1) coding dictionary applied.
SAE according to Investigator's assessment.
MedDRA = Medical Dictionary for Regulatory Activities; SAE = serious adverse event.
a. Day relative to start of study treatment. First day of study treatment = Day 1.

The incidence of laboratory test abnormalities was similar in both treatment groups; no subjects met the criteria for Hy's law. Changes in vital signs (including weight), ECGs and physical examinations were similar in both treatment groups. There was a low incidence of subjects who reported new/intensified neurological findings or findings that became abnormal.

CONCLUSIONS: The non-inferiority of pregabalin as compared to levetiracetam was demonstrated in this study with respect to the primary endpoint; 97 (59%) subjects in the pregabalin group and 104 (59%) subjects in the levetiracetam group had ≥50% reduction in 28-day seizure rate during the maintenance phase, as measured from baseline. The lower bound of the 90% CI for the treatment difference (pregabalin-levetiracetam) in the PP analysis set was -8% which was greater than the pre-defined non-inferiority margin of -12% and the weighted Z-Score was 2.322.

There was no significant difference between treatments for the results of the key secondary endpoint, percent change from baseline in 28-day seizure rate during the double-blind phase (titration phase + maintenance phase). The median difference (pregabalin-levetiracetam) and 90% CI in percent change from baseline in 28-day seizure rate during the double-blind phase (titration phase + maintenance phase), as measured from baseline was 4.1 (-2.6, 10.9) with a p-value of 0.3571.

The results of this study comparing pregabalin with levetiracetam show that the effects of pregabalin on ≥50% reduction in 28-day seizure rate remained within agreed bounds for non-inferiority with respect to levetiracetam.

The safety profiles of pregabalin and levetiracetam were consistent with prior clinical trials and current product labeling for both drugs.