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PROPRIETARY DRUG NAME®/GENERIC DRUG NAME:

THERAPEUTIC AREA AND FDA APPROVED INDICATIONS: See. USPI.

NCT NO.: 00292188

PROTOCOL NO.: A0081064

PROTOCOL TITLE: A 9-Week, Randomized, Double-Blind, Placebo-Controlled, Multicenter, Study of Pregabalin (BID) in Subjects with Post Traumatic Peripheral Neuropathic Pain

Study Centers: Belgium (6), Canada (4), Denmark (2), Finland (2), Italy (3), UK (4), Sweden (3), Romania (3), Portugal (8), Netherlands (5) and Switzerland (1)

Study Initiation and Completion Dates: 25 January 2006 to 27 May 2008

Phase of Development: Phase 3b;

Study Objectives:

Primary

To evaluate the efficacy of pregabalin compared to placebo in the treatment of post-traumatic peripheral neuropathic pain.

Secondary

To evaluate the effects of pregabalin in comparison to placebo on co-morbid symptoms, particularly anxiety, in subjects with post-traumatic peripheral neuropathic pain.

METHODS

Study Design: This study was a 9-week, double-blind, placebo-controlled, multicenter study of pregabalin in subjects with post-traumatic peripheral neuropathic pain. Subjects were randomized to 1 of 2 treatment groups in a 1:1 ratio, pregabalin or matching placebo, respectively. To be randomized subjects must have completed at least 4 diaries and have had a mean pain score of at least 4 points and a visual analogue scale (VAS) score of at least 40 points. The subjects were asked to attend a minimum of 8 visits with the option of 1 additional visit for dose adjustment. The study comprised 4 phases:

1. A 2-week screening period and single-blind washout and placebo run-in phase followed by:

2. A 4-week randomized, dose adjustment, double-blind treatment phase (either pregabalin 150 to 600 mg/day or matching placebo).

    - Dose was adjusted upward from 150 to 600 mg/day, based on tolerability, on a weekly basis (Visits 3 through 5b).

    - Upward dose adjustments occurred in increments of 150 or 300 mg/day.

    - If intolerable adverse events (AEs) occurred at any time during the dose adjustment phase, the dose could be decreased by 1 level (eg, by 150 mg/day). Once a dose reduction had occurred, no further dose adjustments were allowed. Visit 5b was the last scheduled visit for dose adjustment followed by:

3. A 4-week randomized maintenance phase double-blind treatment (either pregabalin 150 mg/day or 300 mg/day or 600 mg/day, or matching placebo).

    - Subjects maintained the same dosing regimen achieved at the end of the dose adjustment phase until the end of Week 8 (Visit 7) followed by:

4. A 1-week double-blind taper phase (either pregabalin 150 to 300 mg/day or matching placebo).

At the completion of the dose maintenance phase, subjects tapered off study medication.

Number of Subjects (Planned and Analyzed):

Planned: Double-Blind: 260 subjects

Analyzed: Single-blind: 252 subjects (efficacy) and 365 subjects (safety)

Double-blind: 252 subjects (efficacy) and 254 subjects (safety)

Diagnosis and Main Criteria for Inclusion: Male or female subjects aged 18 to 80 years with post-traumatic peripheral neuropathic pain persisting for a minimum of 3 months following a traumatic event, with a mean score of ≥4 over the screening period for the daily pain rating scale and ≥40 mm on the VAS. Subjects with neuropathic pain not caused by trauma or central neuropathic pain were excluded.

Study Treatment: All subjects received placebo capsules for the 2-week screening period, subjects were then randomized to placebo or pregabalin treatment. Subjects received pregabalin at a starting dose of 150 mg/day (75 mg twice daily [BID]) or matching placebo for Week 1 and pregabalin 300 mg/day (150 mg BID) or matching placebo for Week 2. The dose could be adjusted from 150 to 600 mg/day based on tolerability during Visits 3 through 5.

During the 4-week randomized maintenance phase, subjects maintained the same dosing regimen achieved at the end of the dose adjustment phase (either pregabalin 150 mg/day or 300 mg/day or 600 mg/day, or matching placebo) until the end of Week 8 (Visit 7).

At the completion of the dose maintenance phase, subjects tapered off study medication during a 1-week double-blind taper phase (either pregabalin 150 to 300 mg/day or matching placebo).

Efficacy Evaluations: *Daily Pain Rating Scale*: The daily pain rating scale (DPRS) consists of an 11-point numerical scale ranging from 0 (no pain) to 10 (worst possible pain). The subjects described their pain during the past 24 hours by choosing the appropriate number between 0 and 10. Self-assessment was performed daily on awakening.

Daily Sleep Interference Scale: The daily sleep interference scale (DSIS) consists of an 11-point numerical scale ranging from 0 (pain does not interfere with sleep) to 10 (pain completely interferes with sleep) allowing the subject to describe how pain interfered with their sleep during the past 24 hours. Self-assessment was performed daily on awakening.

Hospital Anxiety and Depression Scale: The hospital anxiety and depression scale (HADS) is a self-reported scale used to screen for the presence of depressive disorders in non-psychiatric populations. It contains14 items rated on a 4-point Likert-type scale. There are 2 subscales, 1 assessing depression and the other anxiety. The 7-item depression subscale yields a score of 0 to 21 which is interpreted with the following cut-off points:
0 to 7 = normal; 8 to 10 = mild mood disturbance; 11 to 14 = moderate mood disturbance; and 15 to 21 = severe mood disturbance. This scale was completed at screening, baseline and Weeks 1, 5 and 8/early termination (Visits 1, 2, 3, 6 and 7/or early termination).

Medical Outcome Study Sleep Scale: The copyright protected medical outcome study sleep (MOS-Sleep) scale subject-reported measure consists of 12 items that assess the key constructs of sleep. The scale has been found reliable and valid with good overall measurement properties. Subjects are asked to recall sleep-related activities over the past week. Instrument scoring results in 7 subscales: sleep disturbance (4 items), snoring (1 item), awaken short of breath or with headache (1 item), quantity of sleep (1 item), optimal sleep (1 item), sleep adequacy (2 items), somnolence (3 items). Two index measures that assess sleep disturbance can also be constructed (6 items and/or 9 items) to provide composite scores. The MOS-Sleep scale was administered to each subject at baseline and Week 8/early termination (Visits 2 and 7/or early termination).

Medical Outcome Study Cognitive Scale: The MOS-Cognitive (MOS-Cog) scale is a 6-item scale from the Mental Health conceptual area from the RAND Corporation MOS core measures. It assesses confusion, thinking, concentration, attention, memory, and reasoning. The MOS-Cog scale was administered to subjects at baseline and Week 8/early termination (Visits 2 and 7/or early termination). The recall period was 1-week.

Clinical Global Impression of Change: The clinical global impression of change (CGIC) is the clinician's judgment of the overall change in the subject's condition over a defined period on a 7-point scale ranging from 1 (very much improved) to 7 (very much worse). This

assessment was performed at baseline and Week 8/early termination (Visits 2 and 7/or early termination).

Patient Global Impression of Change: The patient global impression change (PGIC) is a subject-rated instrument that measures change in a subjects overall status on a 7-point scale ranging from 1 (very much improved) to 7 (very much worse). This assessment was performed at baseline and Week 8/early termination (Visits 2 and 7/or early termination).

Short-Form McGill Pain Questionnaire Visual Analogue Scale: The Short-Form McGill Pain Questionnaire (SF-MPQ) consists of a VAS to provide overall intensity scores. The subject completed this at baseline (Visit 2) only.

Modified Brief Pain Inventory-Short Form: The modified brief pain inventory-short form (m-BPI-sf) is a self-administered questionnaire developed to assess the severity of pain and the impact of pain on daily functions during a 24-hour period prior to evaluation. It consists of 5 questions, Questions 2, 3, and 4 measures pain (no pain to worst pain possible) on an 11-point scale. Question 5 consists of 7-item subsets A to G, which measure the level of interference of pain on daily functions (does not interfere to completely interferes) on an 11-point scale. This m-BPI-sf was completed by subjects at baseline and Week 8/early termination (Visits 2 and 7/or early termination).

Pain Treatment Satisfaction Scale: The pain treatment satisfaction scale (PTSS) is a validated measure of subject satisfaction for subjects receiving treatment for either acute or chronic pain. The full instrument is 39 items grouped in 5 dimensions (information, medical care, impact of current pain medication, satisfaction with pain medication and side-effects). A modular approach for this instrument has been validated. In this study, the following modules were measured at baseline and Week 8/early termination (Visits 1 and 7/or early termination): impact of current pain medication and satisfaction with current pain medication.

Neuropathic Pain Symptom Inventory: The neuropathic pain symptom inventory (NPSI) is a self-administered questionnaire designed to evaluate the different symptoms of neuropathic pain. It includes 10 descriptors quantified on a 0 to 10 numerical scale and 2 temporal items assessing the duration of spontaneous ongoing and paroxysmal pain. The questionnaire generates a total score and 5 clinically relevant dimensions of neuropathic pain syndromes: burning (superficial) spontaneous pain, pressing (deep) spontaneous pain, paroxysmal pain, evoked pain, and paresthesia/dysesthesia. The scores are discriminative and sensitive to treatment effect. The NPSI was assessed at baseline and Week 8/early termination (Visits 2 and 7/or early termination).

Davidson Trauma Scale: The Davidson trauma scale (DTS) is a self-rated instrument developed specifically for use in diagnosing and measuring symptom severity and treatment outcome in subjects with post-traumatic stress disorder (PTSD). The scale consists of 17 PTSD symptoms as listed by DSM-IV with each item rated on a scale of 0 to 4 for frequency (not at all to every day) and severity (not at all distressing to extremely distressing). Symptoms are rated for the previous week. The total DTS score ranges from 0 to 136. Subscores are computed for 3 symptom clusters: intrusion, avoidance/numbing

and hyper-arousal. The scale has previously demonstrated good sensitivity to variations in symptoms severity and treatment effect. It has also been shown to distinguish between individuals with a current diagnosis of PTSD and those without. It was assessed at baseline and Week 8/early termination (Visits 2 and 7/or early termination).

Pharmacokinetic, Pharmacodynamic, and/or Other Evaluations: (Not Applicable)

Safety Evaluations: Subjects were assessed for adverse events and vital signs (weight, blood pressure, pulse and temperature) at all visits. Height and 12-lead ECGs were recorded at screening only. Laboratory assessments were performed at screening and the final visit.

Statistical Methods: All testing was 2-sided. For each efficacy endpoint, pregabalin was considered statistically significantly different from placebo (pregabalin minus placebo) if the p-value for the comparison was <0.05.

The full analysis set (FAS): consisted of all randomized subjects who received at least 1 dose of study medication and had post-randomization efficacy data.

The per protocol population (PP): consisted of all subjects in the FAS, who did not have any major protocol deviations.

The safety population: consisted of all enrolled subjects who received at least 1 dose of study medication.

Primary Analyses: Weekly Mean Pain Score from the Daily Pain Diary at the End of Treatment (Week 8): The primary analysis was based on the FAS, and compared the weekly mean pain score at Week 8 between the pregabalin (all doses) and placebo groups using an analysis of covariance (ANCOVA) including pooled country (Finland, Switzerland and Italy were pooled, all other countries were fitted without pooling) and baseline mean pain score as covariates. This analysis was also carried out using the PP population.

If a significant result was obtained in the primary analysis, tests for generalizability and sensitivity were also performed using the FAS:

Secondary Analyses: All secondary endpoints were summarized and/or analyzed on the FAS only.

Weekly mean pain score from daily pain diary: A repeated measures analysis was carried out on the weekly mean pain score over time as an exploratory analysis. The covariance between weekly scores was modeled using an unstructured covariance matrix. Fixed effects terms for treatment, baseline score, pooled country, week and week-by-treatment interaction were included in the model.

Weekly Mean Pain Score 30% and 50% Responder rate: The 30% and 50% responder rates (proportion of subjects with a ≥30% and ≥50% reduction in their weekly mean pain score between baseline and endpoint [Week 8]) were summarized using the absolute and relative frequencies. The 30% and 50% responder rates at Week 8 were analyzed using a logistic regression model with treatment, pooled country and baseline value included as covariates.

Weekly mean sleep interference score from daily sleep diary: As for the primary endpoint, the weekly mean sleep interference score at Week 8 was analyzed using an ANCOVA, including terms for treatment, baseline mean sleep interference score and pooled country.

A repeated measures analysis was carried out on the weekly mean sleep interference score over time as an exploratory analysis. The covariance between weekly scores was modeled using an unstructured covariance matrix. Fixed effects terms for treatment, baseline score, pooled country, week and week-by-treatment interaction were included in the model.

Hospital Anxiety and Depression Scale (HADS): The HADS anxiety and depression subscales at Week 8 were analyzed using an ANCOVA, with treatment, pooled country and baseline score included as covariates. The analyses of each subscale were also carried out on the subset of subjects with a baseline score of >10 (ie, moderate/severe anxiety and depression) in that subscale at baseline. All analyses were conducted using a last observation carried forward (LOCF) approach.

Medical Outcome Study Sleep Subscale (MOS-Sleep): The optimal sleep subscale at Week 8 was analyzed using a logistic regression model with treatment, pooled country and baseline value included as covariates. The remaining 6 subscales, the 6-item and 9-item index score were analyzed at Week 8 using ANCOVA with treatment, pooled country and corresponding baseline values included in the model as covariates. All analyses were conducted using a LOCF approach.

Medical Outcome Study Cognitive Subscale (MOS-Cog): The number and percentage of responses to each of the 6 questions was summarized at baseline and Week 8. No formal statistical modeling was used.

Pain Treatment Satisfaction Scale (PTSS): The mean scores from the "impact of current pain medication" and "satisfaction with current pain medication" scales as well as the 2 subscales (medication characteristics and efficacy), were summarized at screening and Week 8. No formal statistical modeling was used.

Modified Brief Pain Inventory Short Form (m-BPI-sf): The pain severity index and the pain interference index scores were summarized at baseline and Week 8. No formal statistical modeling was used. The summaries of these 2 indices were also carried out on the subset of subjects with an mBPI-sf sleep interference-item score >5 at baseline.

Neuropathic Pain Symptom Inventory (NPSI): The Week 8 overall intensity score was analyzed using ANCOVA with treatment, pooled country and baseline score included in the model as covariates. All analyses were conducted using a LOCF approach.

Patient Global Impression of Change (PGIC) and Clinical Global Impression of Change (CGIC): The PGIC and CGIC responses were summarized at baseline and Week 8 using counts and percentages; and analyzed at Week 8 using the Cochran-Mantel-Haenszel (CMH) procedure, adjusted for pooled country. Analyses were conducted using a LOCF approach.

Davidson Trauma Scale (DTS): The Week 8 severity and frequency subscale scores and the total score were analyzed using an ANCOVA, including treatment, pooled country and baseline score as covariates. All analyses were conducted using a LOCF approach.

Short Form McGill Pain Questionnaire – Visual Analogue Scale (sf-MPQ-VAS): The sf-MPQ VAS score recorded at baseline was summarized. No formal statistical modeling was used.

RESULTS

Subject Disposition and Demography: Subject disposition is summarized in Table S1. Of the 367 subjects who received single-blind placebo, 254 subjects were randomized and received double-blind treatment, 127 subjects received pregabalin and 127 subjects received double-blind placebo post randomization. Sixty (23.6%) subjects discontinued from the double-blind treatment; 31 pregabalin-treated subjects and 29 placebo-treated subjects. All double-blind treated subjects were included in the safety analysis, 2 subjects were excluded from the FAS.

Table S1. Subject Disposition

	Single-Blind	Double-Blind	
	Placebo	**Pregabalin**	**Placebo**
Screened 374			
Assigned to study treatment	368		
Treated	367	127	127
Completed	254 (69.2)	96 (75.6)	98 (77.2)
Discontinued	113 (30.8)	31 (24.4)	29 (22.8)
Related to study treatment	8 (2.2)	25 (19.7)	18 (14.2)
AE	5 (1.4)	23 (18.1)	6 (4.7)
Laboratory abnormality	1 (0.3)	0	0
Lack of Efficacy	2 (0.5)	2 (1.6)	12 (9.4)
Not related to study treatment	105 (28.6)	6 (4.7)	11 (8.7)
AE	9 (2.5)	2 (1.6)	3 (2.4)
Laboratory abnormality	4 (1.1)	0	1 (0.8)
Lost to follow-up	3 (0.8)	1 (0.8)	0
Other	77 (21.0)	3 (2.4)	4 (3.1)
Subject no longer willing to participate in study	12 (3.3)	0	3 (2.4)
Analyzed for Efficacy			
FAS	252 (68.7)	126 (99.2)	126 (99.2)
PP population	153 (41.7)	78 (61.4)	75 (59.1)
Analyzed for Safety[a]			
AEs	365 (99.5)	127 (100)	127 (100)
Laboratory data	59 (16.1)	117 (92.1)	123 (96.9)

AE = adverse event, FAS = full analysis set, PP = per protocol

[a] A placebo randomized subject received pregabalin 150 mg BID in error from 06 to 19 September 2006 during the single-blind placebo screening period, this subject's screening safety data is included with the single-blind placebo data.

Race and age were similar for the pregabalin and placebo groups, approximately 96.1% were white and the mean age was 51.7 years. The percentage of females differed between the pregabalin and placebo groups, and was 60.6% and 40.9% respectively. The most common primary diagnoses were peripheral nerve injury and neuralgia.

The most commonly reported concomitant medications across all groups were paracetamol, amitripyline, tramadol and acetylsalicylic acid.

The median duration for subjects receiving double-blind pregabalin was 63 days compared to 64 days for placebo, with the majority of subjects receiving between 61 and 90 days treatment.

Efficacy Results: *Primary Evaluation: Weekly Mean Pain Score from Daily Pain Diary at the End of Treatment (Week 8)*: The pregabalin treatment group had a statistically significant improvement in weekly mean pain score at Week 8 compared to the placebo treatment group. The mean treatment difference was -0.62 points (95% CI: -1.09, -0.15; p-value = 0.010).

Similar results were observed for the PP population where the mean treatment difference was -0.63 points (95% CI: -1.25, -0.01; p-value = 0.045).

Sensitivity analyses with the endpoint redefined as the mean of the last 7 available pain scores, excluding the day after the last dose, a baseline observation carried forward (BOCF) and duration adjusted average change (DAAC) approach were performed. The results of these analyses were similar to those using the LOCF approach. The mean treatment difference with the endpoint redefined as the mean of the last 7 available pain scores was -0.64 points (95% CI: -1.12, -0.17; p-value = 0.008), for the BOCF approach the mean treatment difference was -0.44 points (95% CI: -0.88, 0.00; p-value = 0.052) and for the DAAC approach the mean treatment difference was -0.42 points (95% CI: -0.73, -0.10; p-value = 0.010).

Models including a baseline-by-treatment interaction term and a country-by-treatment interaction term were performed but were not significant.

Weekly Mean Pain Score 30% and 50% Responder Rate: Higher proportions of pregabalin-treated subjects achieved both ≥30% and ≥50% reductions in pain score compared to placebo-treated subjects (odds ratios were 1.84 and 1.78, respectively), and the odds ratio for the proportion of subjects achieving a ≥30% reduction was statistically significant (p=0.032).

Weekly Mean Sleep Interference Score From Daily Sleep Diary: The pregabalin treatment group had a statistically significant improvement in the weekly mean sleep interference score at Week 8 (LOCF) compared to the placebo group. The mean treatment difference was -0.79 points (95% CI: -1.25, -0.34; p-value = 0.001), using the ANCOVA approach.

The repeated measures analysis showed the mean sleep interference scores decreased with time for both treatment groups. There was a statistically significant improvement in mean sleep interference scores for pregabalin compared to placebo treatment at all weeks.

Hospital Anxiety and Depression Scale (HADS): The pregabalin treatment group had statistically significant improvements in the weekly HADS-anxiety and HADS-depression scores at Week 8 compared to the placebo treatment group. The mean treatment difference for the HADS-anxiety score was -0.84 points (95% CI: -1.60, -0.08; p-value = 0.031) and for the HADS-depression score was -0.97 points (95% CI: -1.61, -0.33; p-value = 0.003).

Hospital Anxiety and Depression Scale (HADS) in Subjects with Moderate/Severe Anxiety Scores at Baseline: At baseline 28.9% of subjects (25.4% pregabalin and 32.5% placebo) had moderate/severe HADS-anxiety scores and 15.9% of subjects (13.5% pregabalin and 18.2% placebo) had moderate/severe HADS-depression scores. There were no statistically significant differences at Week 8 between pregabalin and placebo-treated subjects for either the HADS-anxiety (treatment difference was -1.68 points) or HADS-depression (treatment difference was 0.24 points) scores in subjects with baseline moderate/severe anxiety and depression scores, respectively.

Medical Outcome Study Sleep Subscale (MOS-Sleep): The pregabalin-treated subjects showed statistically significant improvements compared to placebo in MOS-sleep subscales, sleep disturbance, awaken short of breath/headache, sleep adequacy, sleep problems index-6 and index-9. A higher percentage of pregabalin-treated subjects achieved optimal sleep at Week 8 compared to placebo-treated subjects; however the difference was not statistically significant.

Medical Outcome Study Cognitive Subscale (MOS-Cog): The number of subjects reported in each of the 6 categories (all of the time, most of the time, a good bit of time, some of the time, a little of the time, or none of the time) did not substantially change for any of the 6 questions (reasoning, concentration, confusion, memory, attention and thinking) in either the pregabalin or placebo treatment groups.

Pain Treatment Satisfaction Scale (PTSS): Screening values for the PTSS scales and subscales were similar for the pregabalin and placebo treatment groups. Scores decreased for impact of current pain medication, and increased for satisfaction with current pain medication and medication characteristics for both treatment groups. The changes from screening were smaller for the pregabalin treatment group compared to the placebo treatment group for impact of current pain medication, but larger scores for satisfaction with current pain medication. The change from screening to end of treatment in medication characteristics scores was similar for each treatment group. Scores for efficacy increased for the pregabalin treatment group and decreased for the placebo treatment group (53.21 points compared to 37.88 points at Week 8).

Modified Brief Pain Inventory Short Form (m-BPI-sf): The interference index and severity index decreased from baseline for both treatment groups at Week 8 with larger decreases observed in the pregabalin treatment group.

Neuropathic Pain Symptom Inventory (NPSI): There was no significant difference in NPSI total intensity score for pregabalin versus placebo at Week 8, the mean treatment difference was -3.84 points (95% CI; -8.28, 0.61; p-value = 0.090).

Patient Global Impression of Change (PGIC) and Clinical Global Impression of Change (CGIC): The CGIC and PGIC comparisons of pregabalin versus placebo at Week 8 showed significant improvements for pregabalin-treated subjects (p-values of 0.007 and 0.006, respectively).

Davidson Trauma Scale (DTS): There was no significant difference between pregabalin and placebo in total DTS score. The mean treatment differences were: -2.95 points (95% CI: -8.33, 2.42; p-value = 0.280) for total DTS score, -2.08 points (95% CI: -4.68, 0.53; p-value = 0.118) for frequency score, and -1.42 points (95%; CI -4.29, 1.45; p-value = 0.331) for severity score.

Short Form McGill Pain Questionnaire – Visual Analogue Scale (sf-MPQ-VAS): The mean sf-MPQ VAS scores at baseline were similar for pregabalin- (63.80 points, 95% CI: 60.98, 66.63) and placebo-treated subjects (66.65 points; 95% CI: 63.65, 69.65).

Pharmacokinetic, Pharmacodynamic, and/or Other Results: (Not Applicable)

Safety Results: No deaths were reported during the study, 2 SAEs were reported during the single-blind phase and 6 SAEs during the double-blind phase. A total of 50 subjects discontinued from the study due to an AE (15 during the single-blind and 35 during double-blind phase) and 47 subjects either had a dose reduction or were temporarily discontinued due to an AE (2 during the single-blind and 45 during double-blind phase).

Treatment-emergent AEs are summarized by treatment group in Table S2. During the single-blind phase 78 subjects experienced 122 AEs (39 subjects experienced 56 treatment-related AEs) including 2 SAEs. During the double-blind phase 109 pregabalin-treated subjects experienced 351 AEs (99 subjects experienced 265 treatment-related AEs) including 4 SAES; 74 placebo-treated subjects experienced 193 AEs (54 subjects experienced 123 treatment-related AEs) including 2 SAEs.

Table S2. All Causality and Treatment-Related Treatment-Emergent AEs –Safety Population

	Single-Blind[a]		Double-Blind			
	Placebo (n [%])		Pregabalin (n [%])		Placebo (n [%])	
	AC	TR	AC	TR	AC	TR
Number (%) of Subjects						
Subjects evaluable for AEs	367	367	127	127	127	127
Number of AEs	122	56	351	265	193	123
Subjects with AEs	78 (21.3)	39 (10.6)	109 (85.8)	99 (78.0)	74 (58.3)	54 (42.5)
Subjects with SAEs	2 (0.5)	0	4 (3.1)	2 (1.6)	2 (1.6)	0
Subjects with severe AEs	8 (2.2)	4 (1.1)	21 (16.5)	19 (15.0)	12 (9.4)	6 (4.7)
Subjects discontinued due to AEs	15 (4.1)	4 (1.1)	25 (19.7)	23 (18.1)	10 (7.9)	6 (4.7)
Subjects with dose reduced or temporary discontinuations due to AEs	2 (0.5)	0	35 (27.6)	31 (24.4)	10 (7.9)	7 (5.5)

AE = adverse event, SAE = serious adverse event, AC = all causality, TR = treatment-related

[a] A placebo randomized subject received pregabalin 150 mg BID in error from 06 to 19 September 2006 during the single-blind placebo screening period, this subject's screening safety data is included with the single-blind placebo data.

Except for the number of AEs subjects were counted only once per treatment in each row

SAEs are according to the investigators assessment

The incidence of all causality treatment-emergent AEs occurring in ≥5 subjects is summarized in Table S3. During the single-blind placebo phase the body system classes with the highest incidence of AEs were nervous system disorders (28 subjects [7.6%] which for 18 [4.9%] were treatment-related) and gastrointestinal disorders (22 [6.0%] which for 10 [2.7%] were treatment-related). The most frequently reported AEs were headache (14 [3.8%] which for 8 [2.2%] were treatment-related) and dizziness (10 [2.7%] which for 8 [2.2%] were treatment-related). The majority of AEs reported during the single-blind phase were mild (81 [66.4%]) in severity, 31 (25.4%) were moderate and 10 (8.2%) were severe.

During the double-blind phase the body system classes with the highest incidence of AEs in the pregabalin treatment group were nervous system disorders (78 subjects [61.4%] which for 76 subjects [59.8%] were considered treatment-related), gastrointestinal disorders (44 [34.6%] which for 32 [25.2%] were treatment-related) and general disorders and administration site conditions (36 [28.3%] which for 34 [26.8% were treatment-related). The body system class with the highest incidence of AEs in the placebo treatment group were nervous system disorders (34 subjects [26.8%] which for 27 subjects [21.3%] were treatment-related) (Tables 13.6.2.2 and 13.6.3.2). The most frequently reported AEs for the pregabalin treatment group were dizziness (55 subjects [43.3%] which for 54 [42.5%] were treatment-related) and somnolence (20 [15.7%]) which for all were considered treatment-related). The most frequently reported AEs in the placebo treatment group were headache (14 subjects [11.0%] which for 11 subjects [8.7%] were treatment-related) and dizziness (12 [9.4%]) which for 9 [7.1%] were treatment-related). The majority of AEs

reported by incidence for pregabalin-treated subjects during the double-blind phase were mild (199 [56.7%]) in severity; 117 (33.3%) were moderate and 35 [10.0%] were severe.

Table S3. Incidence of All Causality and Treatment-Related Treatment−Emergent AEs Occurring in ≥5 Subjects – Safety Population

	Single-Blind		Double-Blind			
	Placebo (n [%])		Pregabalin (n [%])		Placebo (n [%])	
Preferred Term (MedDRA (v11.0)	**AC**	**TR**	**AC**	**TR**	**AC**	**TR**
Dizziness	10 (2.7)	8 (2.2)	55 (43.3)	54 (42.5)	12 (9.4)	9 (7.1)
Somnolence	3 (0.8)	3 (0.8)	20 (15.7)	20 (15.7)	8 (6.3)	8 (6.3)
Fatigue	4 (1.1)	3 (0.8)	15 (11.8)	15 (11.8)	10 (7.9)	8 (6.3)
Headache	14 (3.8)	8 (2.2)	15 (11.8)	11 (8.7)	14 (11.0)	11 (8.7)
Dry mouth	5 (1.4)	5 (1.4)	14 (11.0)	14 (11.0)	6 (4.7)	5 (3.9)
Nausea	8 (2.2)	2 (0.5)	12 (9.4)	10 (7.9)	8 (6.3)	5 (3.9)
Disturbance in attention	1 (0.3)	1 (0.3)	9 (7.1)	9 (7.1)	4 (3.1)	4 (3.1)
Edema peripheral	1 (0.3)	1 (0.3)	9 (7.1)	8 (6.3)	3 (2.4)	3 (2.4)
Constipation	1 (0.3)	1 (0.3)	9 (7.1)	6 (4.7)	4 (3.1)	4 (3.1)
Vision blurred	3 (0.8)	3 (0.8)	8 (6.3)	8 (6.3)	3 (2.4)	3 (2.4)
Feeling drunk	0	0	5 (3.9)	5 (3.9)	0	0
Weight increased	1 (0.3)	1 (0.3)	5 (3.9)	5 (3.9)	2 (1.6)	1 (0.8)
Hyperhidrosis	0	0	4 (3.1)	4 (3.1)	1 (0.8)	1 (0.8)
Balance disorder	0	0	4 (3.1)	4 (3.1)	0	0
Memory impairment	0	0	4 (3.1)	4 (3.1)	3 (2.4)	3 (2.4)
Pain	3 (0.8)	1 (0.3)	5 (3.9)	4 (3.1)	0	0
Vertigo	0	0	4 (3.1)	4 (3.1)	1 (0.8)	1 (0.8)
Neuralgia	1 (0.3)	1 (0.3)	5 (3.9)	3 (2.4)	2 (1.6)	1 (0.8)
Diarrhea	5 (1.4)	3 (0.8)	5 (3.9)	2 (1.6)	5 (3.9)	3 (2.4)
Hypertension	1 (0.3)	0	5 (3.9)	3 (2.4)	2 (1.6)	1 (0.8)
Insomnia	1 (0.3)	0	1 (0.8)	0	6 (4.7)	4 (3.1)

Sorted by decreasing frequency in pregabalin-treated subjects

The numbers of AEs leading to permanent discontinuations are summarized by system organ class in Table S4. Overall, 50 subjects discontinued the study due to AEs, 33 subjects discontinued the study due to AEs considered related to study treatment. Of the subjects who discontinued, 25 subjects were receiving pregabalin, 10 placebo and 15 single-blind placebo (Table S1). Three subjects discontinued due to SAEs. For all treatment groups, the system organ class with the highest number of AEs leading to discontinuation was nervous system disorders.

Table S4. Number of AEs Leading to Discontinuations by System Organ Class

	Single-Blind	Double-Blind	
System Organ Class	**Placebo (n [%]) (N=367)**	**Pregabalin (n [%]) (N=127)**	**Placebo (n [%]) (N=127)**
Nervous System Disorders	5	19	6
General Disorders and Administration Site Conditions	4	9	0
Vascular Disorders	0	3	0
Psychiatric Disorders	2	3	2
Gastrointestinal Disorders	5	3	4
Eye Disorders	2	2	0
Injury, Poisoning and Procedural Complications	0	1	0
Respiratory, Thoracic and Mediastinal Disorders	0	1	0
Ear and Labyrinth Disorders	0	0	1
Skin and Subcutaneous Tissue Disorders	0	0	2
Investigations	4	0	1
Infections and Infestations	0	0	1
Musculoskeletal and Connective Tissue Disorders	2	1	1
Cardiac Disorders	1	0	0

Sorted by decreasing frequency for pregabalin

Four pregabalin and 4 placebo-treated subjects experienced SAEs during double-blind treatment (Table S5). Three subjects in the pregabalin treatment group discontinued from the study due to SAEs.

Table S5. Serious Adverse Events

Sex/Age	MedDRA Preferred Term	Related to Study Treatment	Severity	Outcome
Pregabalin				
M/76	Confusional state[a]	No	Severe	Recovered
M/61	Muscle spasms[a]	No	Moderate	Recovered
F/31	Dyspnoea[a] Tremor[a]	Yes	Severe	Recovered
		Yes	Severe	Recovered
M/74	Viral infection[b]	No	Severe	Recovered
Placebo				
M/54	Back pain[b]	No	Severe	Recovered
	Limb injury[b] Fall[b]	No	Severe	Recovered
		No	Moderate	Recovered
M/32	Viral infection[b]	No	Severe	Recovered
M/53	Accidental overdose	No	Severe	Recovered
F/41	Accidental overdose	No	Severe	Recovered

[a]Permanently discontinued

[b]Multiple challenge/rechallenge/interrupt

There were no clinically significant laboratory abnormalities. In the pregabalin treatment group 4 subjects (3.15%) had a weight increase of ≥7% compared to 2 subjects (1.57%) in the placebo treatment group.

CONCLUSIONS: Subjects treated with pregabalin showed a statistically significant improvement in the weekly mean pain score at Week 8 compared to placebo, with a mean treatment difference of -0.62 points (95% CI: -1.09 to -0.15, p-value = 0.010).

Statistically significant improvements for pregabalin versus placebo-treated subjects at Week 8 occurred for the mean sleep interference score, HADS-anxiety, HADS-depression, CGIC and PGIC.

At baseline 28.9% of subjects (25.4% pregabalin and 24.6% placebo) had moderate/severe HADS-anxiety scores and 15.9% of subjects (13.5% pregabalin and 18.2% placebo) had moderate/severe HADS-depression scores. There were no statistically significant differences between pregabalin and placebo-treated subjects at Week 8 for either the HADS-anxiety or HADS-depression scores in subjects with baseline moderate/severe anxiety or depression scores, respectively.

The pattern of AEs was consistent with those recorded in previous studies with pregabalin.