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ORIGINAL ARTICLE

# Efficacy and tolerability of twice-daily pregabalin for treating pain and related sleep interference in postherpetic neuralgia: a 13-week, randomized trial

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ABSTRACT

*Objective:* This trial evaluated the efficacy and safety of pregabalin dosed twice daily (BID) for relief of neuropathic pain associated with postherpetic neuralgia (PHN).

*Research design and methods:* The 13-week, double-blind, placebo-controlled study randomized 370 patients with PHN to pregabalin (150, 300, or 600 mg/day BID) or placebo.

*Main outcome measures:* Primary efficacy measure was endpoint mean pain score from daily pain diaries. Secondary efficacy measures included endpoint mean sleep-interference score from daily sleep diaries and Patient Global Impression of Change (PGIC). Safety evaluations included adverse events (AEs), physical and neurologic examinations, 12-lead ECG, vital signs, and laboratory testing.

*Results:* Pregabalin provided significant, dose-proportional pain relief at endpoint: difference from placebo in mean pain score, 150 mg/day, –0.88, $p = 0.0077$; 300 mg/day, –1.07, $p = 0.0016$; 600 mg/day, –1.79, $p = 0.0003$. Weekly mean pain scores significantly improved as early as week 1. Sleep interference in all pregabalin groups was also significantly improved at endpoint, compared with placebo ($p < 0.001$), beginning at week 1 ($p < 0.01$). At study termination, patients in the 150 ($p = 0.02$) and 600 mg/day ($p = 0.003$) groups were more likely to report global improvement than were those in the placebo group.

Most AEs were mild or moderate. Among pregabalin-treated patients, 13.5% withdrew due to AEs, most commonly for dizziness (16 patients, 5.8%), somnolence (8, 2.9%), or ataxia (7, 2.5%).

*Conclusions:* Pregabalin, dosed BID, reduced neuropathic pain associated with PHN and was well tolerated. It also reduced the extent to which pain interfered with sleep. Pregabalin's effects were seen as early as week 1 and were sustained throughout the 13-week study.

## Introduction

Ten to fifteen per cent of all patients with herpes zoster (HZ) have postherpetic neuralgia (PHN), persistent pain for > 3 months beyond the resolution of the HZ rash[1]. This often chronic pain resulting from HZ is neuropathic in nature. Neuropathic pain is differentiated from nociceptive pain in that

neuropathic pain is a direct result of damage to or dysfunction of the nervous system, while nociceptive pain is a neural response to injury to body tissues. PHN can be intensely painful, significantly interferes with sleep in > 50% of patients, and often impairs physical and psychosocial functioning[2,3].

Treatment for PHN is often suboptimal. Tricyclic antidepressants have been first-choice therapy for PHN[4–7], but their side-effects profiles may render their use in the elderly problematic[4,8,9]. Some opioid analgesics[10] and local anesthetic preparations (lidocaine patch)[11] have shown some efficacy for relief of PHN. Drugs indicated for acute or nociceptive pain, including non-steroidal anti-inflammatories, have been used to treat PHN with limited success. Gabapentin is approved for treatment of PHN in several countries[12], however, gabapentin is relatively difficult to use clinically: it must be started at low doses, titrated to effective doses, and dosed three times daily (TID), adding complications for physicians and patients, which may affect compliance. There is a need for alternative treatments, the efficacy of which are supported by consistent clinical evidence.

Pregabalin is an alpha$_2$-delta ($\alpha_2$-$\delta$) ligand with analgesic, anxiolytic, and anticonvulsant activity. The compound binds potently to the $\alpha_2$-$\delta$ subunit protein of voltage-gated calcium channels[13]. Potent binding at this site reduces calcium influx at nerve terminals and reduces the release of several neurotransmitters, including glutamate, norepinephrine, and substance P, from activated neurons[14–17]. Pregabalin is inactive at $GABA_A$ and $GABA_B$ receptors, is not converted metabolically into GABA or a GABA antagonist, and does not alter GABA uptake or degradation[18,19]. Pregabalin's $T_{max}$ is 1 h, its $T_{½}$ is 6 h, and it exhibits linear pharmacokinetics with low inter-subject variability. Pregabalin dosing does not require lengthy titration, and its starting dosage of 150 mg/day significantly relieves pain in many patients.

Pregabalin – at dosages of 300 or 600 mg/day – has been shown to be safe and well tolerated, to reduce pain, and to improve sleep disturbance associated with chronic neuropathic pain in three studies totaling over 700 patients who had painful diabetic peripheral neuropathy[20–22]. Similarly, dosages of 150, 300, and 600 mg/day (TID) pregabalin were shown to relieve pain and related sleep interference in two PHN studies of over 400 patients[23,24]. Most recently, in a study of 338 patients with either painful DPN or PHN who received 600 mg/day or flexibly-dosed (150–600 mg/day) pregabalin twice daily (BID) or placebo, treatment with pregabalin was associated with significant improvements in both pain and pain-related sleep interference[25]. In 2004, the American Academy of Neurology issued practice parameters for the treatment of PHN which identified pregabalin as a first-line treatment option for PHN[1]. This study was designed to evaluate the efficacy and tolerability of pregabalin dosed BID to enhance its ease of use in patients with PHN across its therapeutic dosing range.

## Patients and methods

Study 1008-196 was a randomized, double-blind, placebo-controlled, parallel-group, fixed-dose, multicenter, phase 3 trial, conducted from November 9, 2001 to October 30, 2002. Patients were randomized to one of four treatments: placebo, 150, 300, or 600 mg/day pregabalin, administered in two doses each day. Because pregabalin is renally excreted (98% as unchanged drug), and because a doubling of exposure can be expected with a 50% reduction in creatinine clearance ($CL_{cr}$)[26], patients randomized to the 600 mg/day group were stratified based on each patient's $CL_{cr}$: in this group, patients with $CL_{cr}$ > 60 mL/min received 600 mg/day pregabalin, while patients who had $CL_{cr}$ > 30 and ≤ 60 mL/min received 300 mg/day, a dosage providing equivalent exposure to 600 mg/day in patients with $CL_{cr}$ > 60 mL/min, based on pharmacokinetic modeling studies[27]. Creatinine clearance was estimated from serum creatinine, body weight, age, and sex using the Cockcroft and Gault equation.

The study consisted of three phases: 1-week baseline, 13-week double-blind treatment (including 1-week titration and 12-week fixed-dose phases for patients receiving 300 or 600 mg/day), and 1-week follow-up for patients not entering the open-label extension study. Patients were seen at six scheduled visits plus one follow-up visit (if not entering open label).

The study was conducted in accordance with the International Conference on Harmonization Guidelines for Good Clinical Practice, the Declaration of Helsinki, and US Food and Drug Administration regulations. Written informed consent was required from each patient (or their authorized representative) prior to enrolment. The protocol, consent documents, and protocol amendments were approved by each of the 76 participating centers' Institutional Review Boards.

Patients were eligible if they were ≥ 18 years old, had pain for > 3 months after healing of HZ lesions, had a visual analogue scale pain score ≥ 40 mm at baseline and at randomization, and had at least four daily pain diary entries with a mean daily pain score ≥ 4 prior to randomization. Patients had to be excluded for the following reasons: malignancy (with the exception of basal cell carcinoma) within the past 2 years; WBC < 2500 mm$^3$, neutrophil count < 1500 mm$^3$, or platelet count < 100 × 10$^3$/mm$^3$; clinically significant or unstable hepatic, respiratory, or hematologic illnesses or psychologic conditions; unstable cardiovascular disease;

abnormal 12-lead ECG; history of chronic hepatitis B or C, hepatitis B or C within the past 3 months, or HIV infection; immunocompromise; history of alcohol or illicit drug abuse within the last 2 years; or participation in a clinical trial for an investigational drug or agent within 30 days prior to baseline or participation in a previous trial of pregabalin. Patients with $CL_{cr} \leq 30$ mL/min also were to be excluded, as were patients who had previous surgical therapy for PHN, who had other severe pain or skin conditions in the affected dermatome that could alter sensation or that might compromise PHN assessment, or who had used prohibited medications, including long-acting benzodiazepines, skeletal muscle relaxants, steroids, capsaicin, mexiletine, dextromethorphan, amantadine, alpha-lipoic acid, hydroxychloroquine, thioridazine, deferoxamine, and antiepileptics (including carbamazepine, clonazepam, phenytoin, valproic acid, lamotrigine, topiramate, vigabatrin, and gabapentin) without appropriate washout (at least 7 days prior to entry to baseline phase). Stable regimens (of ≥ 30 days prior to study entry; therapy not to be initiated during study period) of non-narcotic analgesics, e.g., noramidopyrine and paracetamol, and stable regimens of opioids, anti-inflammatories, and antidepressants were allowed.

The primary efficacy parameter was endpoint mean pain score, based on the last 7 days of patients' daily pain diaries. Daily pain diaries consisted of an 11-point numerical rating scale (NRS), in which 0 = 'no pain' and 10 = 'worst possible pain'. Each morning, patients rated the severity of their pain during the past 24 h by circling the appropriate number on the NRS. Supplemental analyses of the primary efficacy parameter included proportion of responders (patients with ≥ 50% reduction and patients with ≥ 30% reduction in mean pain score from baseline) and weekly mean pain scores. Secondary efficacy parameters included endpoint mean sleep-interference scores and weekly mean sleep-interference scores. These measures were derived from daily sleep-interference diaries, consisting of an 11-point NRS, with 0 = 'pain does not interfere with sleep' through 10 = 'pain completely interferes with sleep'. At study termination, patients were also administered the Patient Global Impression of Change (PGIC), a patient-rated instrument measuring change in patients' overall health status on a 7-point scale ranging from 1 ('very much improved') to 7 ('very much worse').

Efficacy analyses were performed on a modified intent-to-treat (ITT) population – randomized patients who took at least one dose of study medication and who had one or more post-baseline scores. Patients with no data for a parameter at baseline or at the time-point analyzed were excluded from that analysis. The sample size calculation was based on the primary efficacy parameter. Based on the results of previous pregabalin PHN trials, a common standard deviation of 2.15 was assumed[23,24]. Assuming two-sided testing at the 0.0167 level (to control for multiple comparisons), 88 patients per treatment group would provide over 90% power to detect a difference of at least 1.3 between at least one pregabalin group and placebo. This difference from placebo is consistent with the design of other pregabalin PHN studies. Under the assumption of equal allocation between the four treatment groups, a total sample size of 352 randomized patients is required.

The primary analysis of the primary parameter was an ANCOVA, including effects for treatment, cluster, $CL_{cr}$ stratum, and baseline mean pain score as the covariate. In addition, repeated-measures analysis was performed for the weekly mean pain scores and the weekly mean sleep interference scores. In each case, adjusted (least-squares) means were obtained from the model, and 95% confidence intervals on the difference in least-squares means between each pregabalin treatment group and placebo were constructed. PGIC was analyzed using the Cochran-Mantel-Haenszel (CMH) test with modified ridit scores adjusting for cluster and $CL_{cr}$ stratum. $p$ values were adjusted using the Hochberg procedure for the three pairwise comparisons versus placebo in order to protect the type I error rate at the 0.05 level. All statistical testing was done using SAS Version 6.12. Safety was assessed via adverse events (AEs) reporting (assessed as 'mild', 'moderate', or 'severe' by the investigators), laboratory testing, physical and neurologic exams, and 12-lead ECGs.

## Results

The four treatment groups were similar in gender (54% were female), age (mean = 70.7 ± 10.6 years), duration of PHN (mean = 40.7 months, median = 27 months), height, weight, and $CL_{cr}$ (Table 1). Four hundred and thirty-five patients entered the baseline phase, and 65 withdrew during the baseline phase: one patient experienced an adverse event, 48 patients (11%) did not meet the inclusion criteria, and 16 patients (4%) withdrew due to other/administrative reasons. Three hundred and seventy patients completed the baseline phase and were randomized (2 patients, one assigned to placebo and one to pregabalin 600 mg/day, did not receive study medication after randomization, Figure 1), and 368 patients were included in the modified ITT population. (The results and discussion below refer to this population.) Concurrent medications for pain relief were used by 53% of patients – with paracetamol the most commonly reported (23%), followed by amitriptyline (12%) and tramadol (6%).

***Table 1.*** *Patient characteristics (ITT population)*

| | Placebo ($n$ = 93) | Pregabalin 150 mg/day ($n$ = 87) | Pregabalin 300 mg/day ($n$ = 98) | Pregabalin 300/600 mg/day ($n$ = 90) | All patients ($n$ = 368) |
|---|---|---|---|---|---|
| Gender | | | | | |
| Male, *n* (%) | 40 (43) | 36 (41.4) | 54 (55.1) | 38 (42.2) | 168 (45.7) |
| Female, *n* (%) | 53 (57) | 51 (58.6) | 44 (44.9) | 52 (57.8) | 200 (54.3) |
| Premenopausal, *n* (%) | 1 ( 1.9) | 2 (3.9) | 2 (3.9) | 4 (7.7) | 9 (4.5) |
| Postmenopausal, *n* (%) | 52 (98.1) | 49 (96.1) | 42 (95.5) | 48 (92.3) | 191 (95.5) |
| Race | | | | | |
| White, *n* (%) | 92 (98.9) | 86 (98.9) | 98 (100) | 88 (97.8) | 364 (98.9) |
| Black, *n* (%) | 0 | 1 (1.1) | 0 | 1 (1.1) | 2 (0.5) |
| Other, *n* (%) | 1 (1.1) | 0 | 0 | 1 (1.1) | 2 (0.5) |
| Age categories | | | | | |
| 18–64 years, *n* (%) | 20 (21.5) | 20 (23.0) | 25 (25.5) | 23 (25.6) | 88 (23.9) |
| 65, *n* (%) | 73 (78.5) | 67 (77.0) | 73 (74.5) | 67 (74.4) | 280 (76.1) |
| Age (years) | | | | | |
| Mean (SD) | 70.9 (10.4) | 70.5 (9.3) | 70.7 (11.9) | 70.7 (10.6) | 70.7 (10.6) |
| Median | 72.0 | 73.0 | 73.0 | 72.5 | 73.0 |
| Min–max | 42–89 | 38–88 | 18–92 | 38–90 | 18–92 |
| Weight (kg) | | | | | |
| Mean (SD) | 73.03 (15.95) | 72.27 (14.72) | 73.72 (14.07) | 72.71 (14.72) | 72.96 (14.82) |
| Median | 72.00 | 72.00 | 74.35 | 71.45 | 72.00 |
| Min–max | 36.0–154.0 | 44.8–111.1 | 45.0–111.0 | 44.5–105.8 | 36.0–154.0 |
| Baseline mean pain score | | | | | |
| Mean (SD) | 6.85 (1.49) | 6.44 (1.58) | 6.72 (1.41) | 6.65 (1.44) | 6.67 (1.48) |
| Median | 7 | 6.57 | 6.93 | 6.71 | 6.79 |
| Min–max | 1.71–10.00 | 2.57–10.00 | 3.71–9.71 | 3.86–10.00 | 1.71–10.00 |
| Duration of PHN (months) | | | | | |
| Mean (SD) | 43.3 (44.8) | 36.3 (43.1) | 48.2 (53.1) | 34.1 (37.3) | 40.7 (45.3) |
| Median | 31 | 22 | 29 | 22.5 | 27 |
| Min–max | 2–263 | 2–224 | 3–262 | 2–180 | 2–263 |
| Baseline $CL_{cr}$ (mL/min) | | | | | |
| Mean (SD) | 76.80 (31.68) | 74.34 (21.13) | 75.33 (26.26) | 76.34 (25.90) | 75.71 (26.50) |
| Median | 68.00 | 71.00 | 70.50 | 72.50 | 71.00 |
| Min–max | 32.0–229.0 | 36.0–126.0 | 37.0–201.0 | 33.0–152.0 | 32.0–229.0 |
| $CL_{cr}$ stratum | | | | | |
| Low (30-60 mL/min), *n* (%) | 31 (33.3) | 26 (29.9) | 33 (33.7) | 26 (28.9) | 116 (31.5) |
| Normal (> 60 mL/min), *n* (%) | 62 (66.7) | 61 (70.1) | 65 (66.3) | 64 (71.1) | 252 (68.5) |

Thirty-four per cent of patients who received study medication withdrew during the double-blind phase: 13% because of an AE, 16% for lack of efficacy, 1% for lack of compliance, and 6% for other reasons (Figure 1). Two hundred and seventy-five patients (75%) entered the open-label, follow-on study: 63 (70%) from the pregabalin 600 mg/day, 70 (71%) from the 300 mg/day, 68 (78%) from the 150 mg/day, and 74 (80%) from the placebo groups.

Endpoint mean pain score was significantly improved for each pregabalin dosage group compared with placebo (Table 2). Mean pain scores were also analyzed at each study week, and, compared with placebo, all three pregabalin groups demonstrated significantly superior improvements in weekly mean pain score beginning at Week 1 ($p$ = 0.0005 for 150 mg/day; $p$ = 0.0002 for 300 and 600 mg/day). These significant improvements were maintained at every weekly timepoint and persisted throughout the study's 13-week duration (Figure 2), with maximum treatment effect beginning at approximately week 3.

The proportion of 50% responders (≥ 50% reduction from baseline) was 26.4% for the 150 mg/day, 26.5% for the 300 mg/day, and 37.5% for the 600 mg/day pregabalin groups versus 7.5% for the placebo group ($p$ = 0.001 for each pregabalin group compared with placebo). The number needed to treat (NNT) based on ≥ 50% responder rates was 5.3 for the 150 mg/day, 5.3 for the 300 mg/day, and 3.3 for the 600 mg/day pregabalin groups. The NNT for all pregabalin dosages combined (150–600 mg/day), was 4.4. The proportion

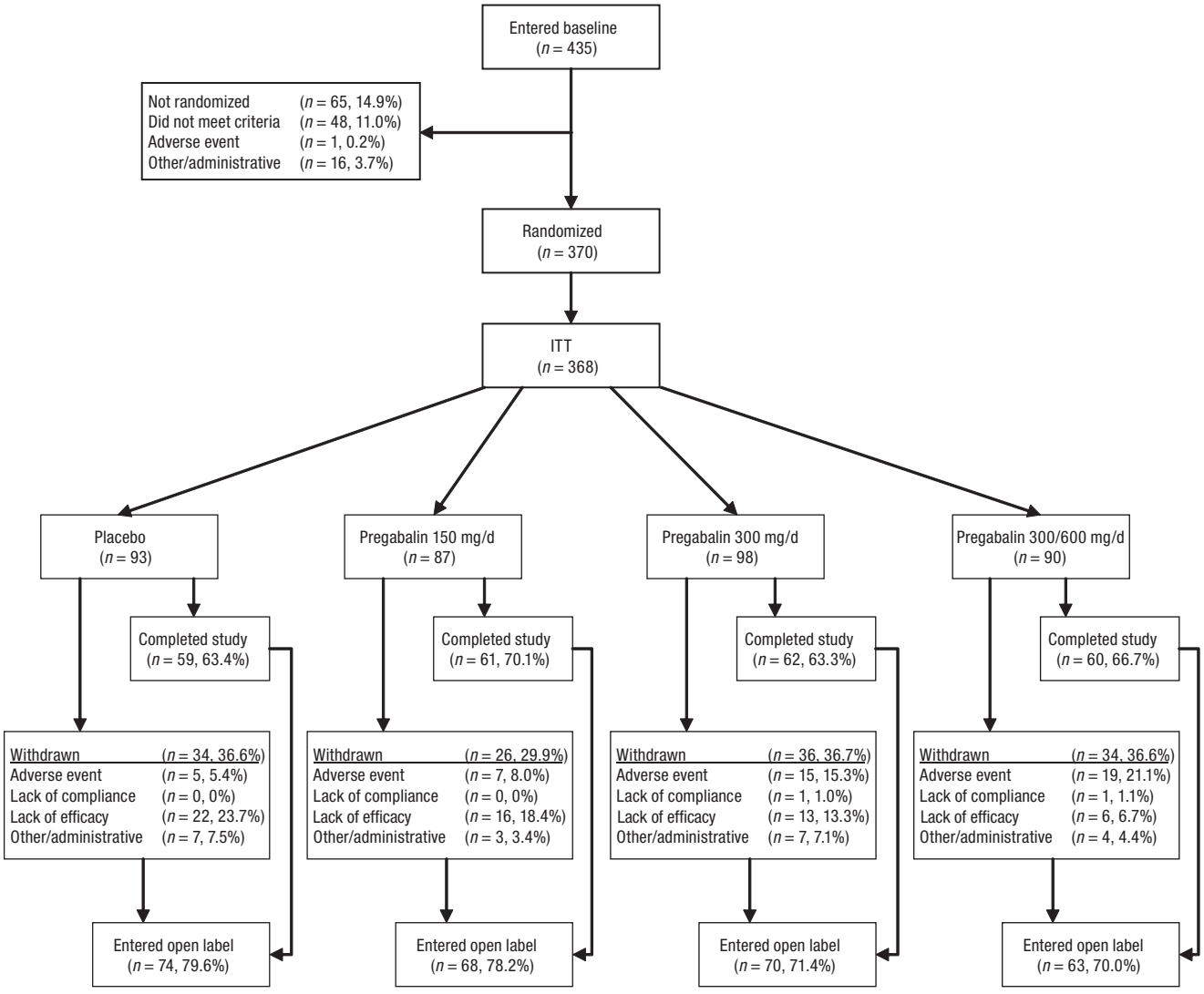


***Figure 1.*** *Patient disposition cohort diagram*

***Table 2.*** *Endpoint* mean pain and sleep interference scores for patients treated with placebo and three dosages of pregabalin (PGB)*

| | *N* | Least-squares means | SE | Treatment comparisons, pregabalin vs. placebo | | | |
|---|---|---|---|---|---|---|---|
| | | | | Difference | 95% CI | Unadjusted *p* value | Adjusted† *p* value |
| Pain | | | | | | | |
| Placebo | 93 | 6.14 | 0.23 | | | | |
| PGB 150 | 87 | 5.26 | 0.24 | –0.88 | (–1.53, –0.23) | 0.0077 | 0.0077 |
| PGB 300 | 98 | 5.07 | 0.23 | –1.07 | (–1.70, –0.45) | 0.0008 | 0.0016 |
| PGB 600 | 88 | 4.35 | 0.24 | –1.79 | (–2.43, –1.15) | 0.0001 | 0.0003 |
| Sleep | | | | | | | |
| Placebo | 93 | 4.10 | 0.21 | | | | |
| PGB 150 | 87 | 3.07 | 0.22 | –1.03 | (–1.62, –0.44) | 0.0007 | 0.0007 |
| PGB 300 | 98 | 2.84 | 0.21 | –1.26 | (–1.84, –0.68) | 0.0001 | 0.0002 |
| PGB 600 | 88 | 2.17 | 0.22 | –1.93 | (–2.52, –1.34) | 0.0001 | 0.0002 |

SE = standard error; CI = confidence interval; PGB = pregabalin

*Endpoint = last 7 available scores while on study medication, up to and including the day after the last dose. Based on LS Means using ANCOVA model (including effects for treatment, cluster, $CL_{cr}$ stratum, and the baseline score value as covariate)

†Adjustment based on Hochberg's procedure

of patients with ≥ 30% pain reduction from baseline, a clinically meaningful degree of improvement, as reported by Farrar *et al.*[28], was 39.1% for the 150 mg/day, 40.8% for the 300 mg/day, and 52.3% for the 600 mg/day pregabalin groups versus 17.2% for placebo ($p \leq 0.001$, Figure 3).

Mean sleep-interference scores at endpoint were significantly improved, compared with placebo, in all three pregabalin groups ($p = 0.0007$ for 150 mg/day; $p = 0.0002$ for 300 and for 600 mg/day, Table 2). Weekly mean sleep-interference scores were significantly better than placebo beginning at week 1

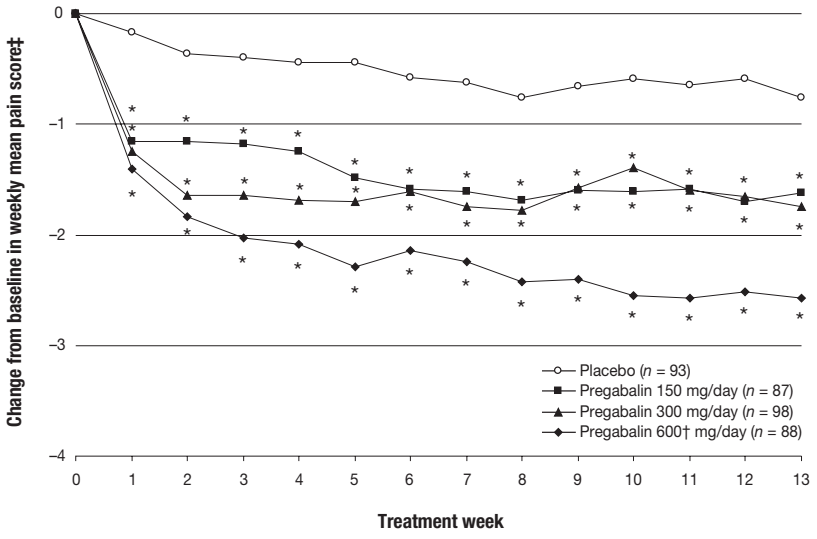


***Figure 2.*** *Change from baseline in weekly mean pain scores, weeks 1–13. *p ≤ 0.01 vs. placebo. †600 mg/day arm stratified according to $CL_{cr}$. Patients with $CL_{cr} > 30$ and ≤ 60 mL/min received 300 mg/day pregabalin; patients with $CL_{cr} > 60$ mL/min received 600 mg/day. ‡Greater negative change from baseline indicates greater pain relief*

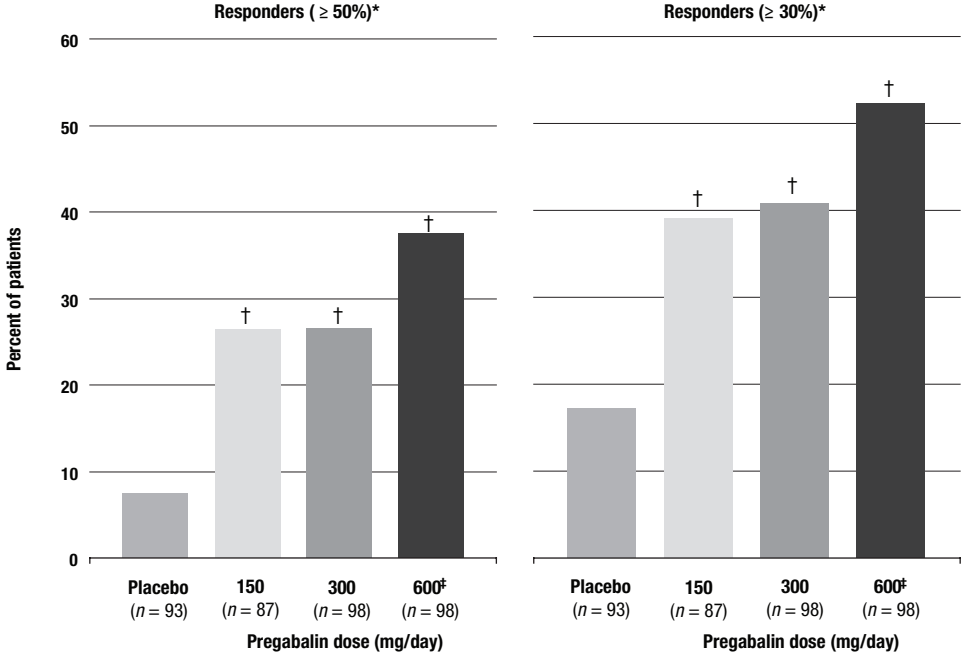


***Figure 3.*** *Proportion of responders to treatment. *≥ 50% and ≥ 30% reduction from baseline. †p ≤ 0.001 vs. placebo. ‡600 mg/day arm stratified according to $CL_{cr}$. Patients with $CL_{cr} > 30$ and ≤ 60 mL/min received 300 mg/day; patients with $CL_{cr} > 60$ mL/min received 600 mg/day*

and for every study week thereafter ($p < 0.01$ for all pregabalin groups, Figure 4).

At study termination, patients in the 150 ($p = 0.02$) and 600 mg/day ($p = 0.003$) groups were more likely to report global improvement than those in the placebo group. At least minimal improvement was reported by 51.2%, 47.9%, and 67.1% of patients treated with 150, 300, and 600 mg/day pregabalin, respectively compared with 35.6% of those treated with placebo. Much or very much improvement was reported by 22.6%, 27.2%, and 36.5% of patients treated with 150, 300, and 600 mg/day pregabalin, compared with 16.2% of those receiving placebo.

## Safety and tolerability

The most commonly reported treatment-associated AEs (Table 3) for the pregabalin groups were dizziness (16.1%, 32.7%, 36.7% of patients in the 150, 300, and 600 mg/day groups, respectively; 9.7% for placebo), somnolence (9.2%, 11.2%, 25.6% of patients in the 150, 300, and 600 mg/day groups, respectively; 4.3% for placebo), and peripheral edema (12.6%, 14.3%, 13.3% of patients in the 150, 300, and 600 mg/day groups, respectively; 10.8% for placebo). Most AEs were mild or moderate in intensity. There were no patient deaths reported during this double-blind study. Sixteen per cent of the 275 patients in the three pregabalin groups and 13% of the 93 placebo-group patients had severe AEs. Serious AEs (defined as congenital anomaly/birth defect, persistent or significant disability/incapacity, any AE resulting in patient hospitalization or prolongation of existing hospitalization, immediately life-threatening, death, or any medically significant event, including laboratory abnormalities) occurred in 3.6% of pregabalin patients and 2.2% of placebo patients. A total of 13.5% of pregabalin patients and 4.3% of placebo patients withdrew because of AEs considered associated with treatment. Among pregabalin-treated patients, AEs most frequently leading to withdrawal were dizziness (5.8%), somnolence (2.9%), and ataxia (2.5%), while among placebo-treated patients, dizziness (3.2%) most frequently led to withdrawal (no patients in the placebo group withdrew because of somnolence or ataxia). Only 1.5% of pregabalin-treated patients and 1.1% of placebo-treated patients withdrew from the study because of peripheral edema. Of pregabalin-treated patients, 6.9% reported weight gain as an AE that was considered associated with treatment. None of the AEs of weight gain was considered severe, and none led to withdrawal from the study.

Two patients had abnormal ECG findings that were present at termination, with no previous clinically significant findings detected at baseline. One patient's abnormal ECG findings were considered unrelated to pregabalin (the patient had a history of hypertension and stroke and showed evidence of myocardial infarction at baseline); findings for the other patient (who was in the placebo group) were considered of unknown causality. Neither of these findings led to withdrawal.

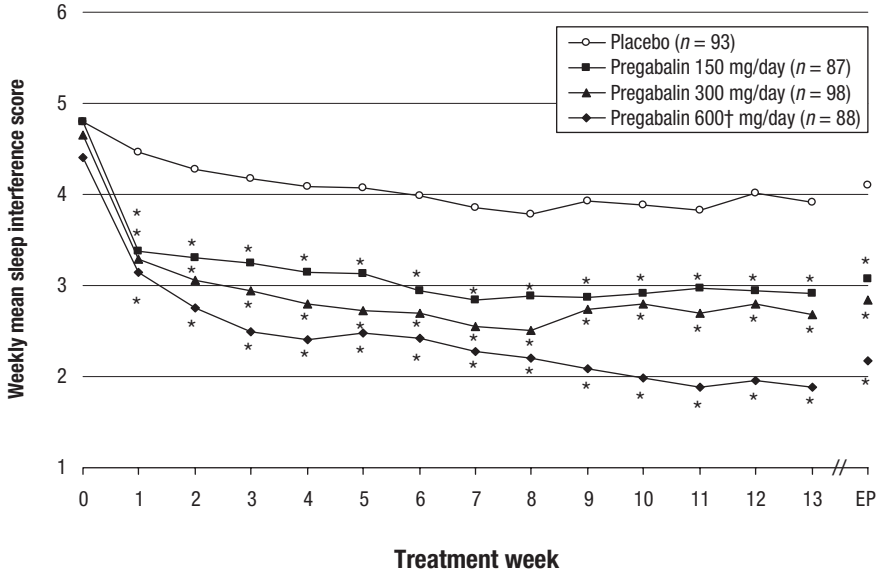


***Figure 4.*** *Mean weekly pain-related sleep-interference scores in postherpetic neuralgia at all dosages. *p ≤ 0.01 vs. placebo. †600 mg/day arm stratified according to $CL_{cr}$. Patients with $CL_{cr} > 30$ and ≤ 60 mL/min received 300 mg/day pregabalin; patients with $CL_{cr} > 60$ mL/min received 600 mg/day*

***Table 3.*** *Summary of associated* treatment-emergent adverse events (ITT population)*

| Adverse event/preferred term | Placebo (*N* = 93) | | Pregabalin 150 mg/day (*N* = 87) | | Pregabalin 300 mg/day (*N* = 98) | | Pregabalin 600 mg/day (*N* = 90) | |
|---|---|---|---|---|---|---|---|---|
| | Number of patients (%) | | | | | | | |
| Dizziness | 9 | (9.7) | 14 | (16.1) | 32 | (32.7) | 33 | (36.7) |
| Somnolence | 4 | (4.3) | 8 | (9.2) | 11 | (11.2) | 23 | (25.6) |
| Peripheral edema | 10 | (10.8) | 11 | (12.6) | 14 | (14.3) | 12 | (13.3) |
| Ataxia | 0 | (0.0) | 3 | (3.4) | 6 | (6.1) | 11 | (12.2) |
| Dry mouth | 0 | (0.0) | 5 | (5.7) | 4 | (4.1) | 11 | (12.2) |
| Constipation | 2 | (2.2) | 1 | (1.1) | 8 | (8.2) | 8 | (8.9) |
| Weight gain | 0 | (0.0) | 3 | (3.4) | 8 | (8.2) | 8 | (8.9) |
| Amblyopia | 1 | (1.1) | 2 | (2.3) | 3 | (3.1) | 5 | (5.6) |
| Asthenia | 5 | (5.4) | 4 | (4.6) | 3 | (3.1) | 5 | (5.6) |
| Edema | 3 | (3.2) | 3 | (3.4) | 3 | (3.1) | 5 | (5.6) |
| Abnormal gait | 0 | (0.0) | 1 | (1.1) | 2 | (2.0) | 4 | (4.4) |
| Abnormal vision | 0 | (0.0) | 0 | (0.0) | 2 | (2.0) | 4 | (4.4) |
| Face edema | 2 | (2.2) | 3 | (3.4) | 1 | (1.0) | 4 | (4.4) |
| Headache | 3 | (3.2) | 4 | (4.6) | 1 | (1.0) | 4 | (4.4) |
| Thinking abnormal | 1 | (1.1) | 2 | (2.3) | 2 | (2.0) | 4 | (4.4) |
| Confusion | 1 | (1.1) | 3 | (3.4) | 3 | (3.1) | 3 | (3.3) |
| Diplopia | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 3 | (3.3) |
| Flatulence | 2 | (2.2) | 1 | (1.1) | 0 | (0.0) | 3 | (3.3) |
| Incoordination | 0 | (0.0) | 2 | (2.3) | 1 | (1.0) | 3 | (3.3) |
| Nausea | 5 | (5.4) | 1 | (1.1) | 0 | (0.0) | 2 | (2.2) |
| Diarrhea | 1 | (1.1) | 5 | (5.7) | 0 | (0.0) | 0 | (0.0) |
| Pain | 2 | (2.2) | 2 | (2.3) | 3 | (3.1) | 0 | (0.0) |
| Sweating | 3 | (3.2) | 1 | (1.1) | 0 | (0.0) | 0 | (0.0) |

*AEs that were possibly, probably, or definitely related – and those for which the relationship was unknown – reported in at least 3% of patients in any treatment group. Events are sorted by decreasing frequency in the 600 mg/day pregabalin treatment group

## Discussion

In this 13-week study of patients with PHN – more than half of whom had high (> 6) baseline mean pain scores despite the use of pain-relief medications – all three BID dosages of pregabalin were associated with a statistically significant reduction in endpoint mean pain score versus placebo. Onset of statistically significant reduction of pain was rapid – beginning as early as Week 1, the first post-baseline time-point analyzed – and remained statistically significant throughout the study's 13 weeks. This finding is consistent with results reported from previous studies of pregabalin in both painful DPN and PHN. Pregabalin showed an increase in effect with increasing dosage. At exposure equivalent to 600 mg/day BID, 37.5% of pregabalin-treated patients met the strict criterion for response (≥ 50% improvement). The NNT for this level of reduction in pain for the dosage range of 150–600 mg/day was 4.4 (consistent with that observed in other studies of pregabalin for neuropathic pain), while the NNT to achieve a similar reduction in pain for gabapentin across a dosage range of 1800–3600 mg/day has been calculated, from two studies, to be 5.0–5.8[12,29]. Further, 52% of patients in the 600 mg/day BID pregabalin group experienced ≥ 30% improvement, a level considered to indicate clinically meaningful pain relief[28].

Improvement of sleep interference began by week 1 for each of the three dosage groups, and it was significantly superior to placebo at each weekly time-point throughout the study. Because sleep interference is frequently co-morbid with PHN (in > 50% of patients)[2], pregabalin's effect on sleep interference represents an important benefit to patients being treated for PHN.

Pregabalin's effect of reducing pain and improving pain-related sleep interference in patients with PHN has been established in two previous studies using TID dosing[23,24] and in one study using BID dosing[25]. In this trial using BID dosing of longer duration (13 weeks versus 8 weeks in the two previous TID-dosing PHN trials), pregabalin demonstrated similar efficacy and tolerability. Further, while the trial reported by Dworkin *et al.*[23] had a single treatment arm (300 or 600 mg/day based on creatinine clearance) and the trial reported by Sabatowksi *et al.*[24] included 150- and 300-mg/day treatment arms, this is the first pregabalin PHN trial to include three treatment arms spanning

pregabalin's effective dosing range, 150–600 mg/day, and each treatment arm was associated with significant efficacy and favorable tolerability. Importantly, even at the high end of pregabalin's dosing range, using a BID as opposed to a TID schedule, most AEs were mild to moderate, and the low withdrawal rate due to AEs suggests the clinical benefit of treatment may have outweighed the discomfort of patients' AEs.

## Conclusion

In addition to confirming previous data demonstrating pregabalin's sustained, beneficial effects for relief of neuropathic pain and associated sleep interference[20–25], this 13-week study supports a more convenient BID dosing schedule in PHN. Pregabalin represents a rapid-onset treatment option for PHN that is easy to use, shows low intersubject variability, and is well tolerated.

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Drs Feister, Stoker, Versavel, and Rigaudy and Mr Young were involved in the study design, analysis and interpretation of data, and preparation of this paper. Mr Young was the senior statistician. All five are or were employees of Pfizer Inc.

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