# A randomized trial of pregabalin in patients with neuropathic pain due to spinal cord injury

Diana D. Cardenas, MD, MHA
Edward C. Nieshoff, MD
Kota Suda, MD
Shin-ichi Goto, MD
Luis Sanin, MD
Takehiko Kaneko, MD
Jonathan Sporn, MD
Bruce Parsons, MD, PhD
Matt Soulsby, PhD
Ruoyong Yang, PhD
Ed Whalen, PhD
Joseph M. Scavone, PharmD
Makoto M. Suzuki, PhD
Lloyd E. Knapp, PharmD

Correspondence to Dr. Cardenas: dcardenas@med.miami.edu

## ABSTRACT

**Objective:** To assess the efficacy and tolerability of pregabalin for the treatment of central neuropathic pain after spinal cord injury (SCI).

**Methods:** Patients with chronic, below-level, neuropathic pain due to SCI were randomized to receive 150 to 600 mg/d pregabalin (n = 108) or matching placebo (n = 112) for 17 weeks. Pain was classified in relation to the neurologic level of injury, defined as the most caudal spinal cord segment with normal sensory and motor function, as above, at, or below level. The primary outcome measure was duration-adjusted average change in pain. Key secondary outcome measures included the change in mean pain score from baseline to end point, the percentage of patients with ≥30% reduction in mean pain score at end point, Patient Global Impression of Change scores at end point, and the change in mean pain-related sleep interference score from baseline to end point. Additional outcome measures included the Medical Outcomes Study–Sleep Scale and the Hospital Anxiety and Depression Scale.

**Results:** Pregabalin treatment resulted in statistically significant improvements over placebo for all primary and key secondary outcome measures. Significant pain improvement was evident as early as week 1 and was sustained throughout the treatment period. Adverse events were consistent with the known safety profile of pregabalin and were mostly mild to moderate in severity. Somnolence and dizziness were most frequently reported.

**Conclusions:** This study demonstrates that pregabalin is effective and well tolerated in patients with neuropathic pain due to SCI.

**Classification of evidence:** This study provides Class I evidence that pregabalin, 150 to 600 mg/d, is effective in reducing duration-adjusted average change in pain compared with baseline in patients with SCI over a 16-week period ($p = 0.003$, 95% confidence interval = −0.98, −0.20).
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## GLOSSARY

**AE** = adverse event; **ANCOVA** = analysis of covariance; **BOCF** = baseline observation carried forward; **CI** = confidence interval; **DAAC** = duration-adjusted average change; **LOCF** = last observation carried forward; **MOS-SS** = Medical Outcomes Study–Sleep Scale; **SCI** = spinal cord injury.

Chronic pain is present in approximately two-thirds of patients after spinal cord injury (SCI), with nearly one-third rating their pain as severe.[1] Chronic central neuropathic pain, which results from damage to the central sensory system itself,[2] occurs in approximately 40% of patients with SCI.[3] This pain is often severe and refractory to treatment, which includes anticonvulsants, antidepressants, analgesics, and antispasticity medications.[4–7] As a result, central neuropathic pain after SCI has a substantial impact on patient function, sleep, and overall quality of life.[8–10]

Pregabalin (Lyrica; Pfizer Inc., New York, NY), an $\alpha_2\delta$ ligand, is approved for the treatment of neuropathic pain in more than 100 countries,[11] including the treatment of central and peripheral neuropathic pain in the European Union,[12] peripheral neuropathic pain in Japan,[11] and peripheral neuropathic pain due to diabetic peripheral neuropathy or postherpetic neuralgia in the United

Supplemental data at www.neurology.org

From the Department of Rehabilitation Medicine (D.D.C.), The Leonard M. Miller School of Medicine, University of Miami, FL; Wayne State University (E.C.N.), Detroit, MI; Pfizer Inc. (L.S., J.S., B.P., R.Y., E.W.), New York; Hokkaido Chuo Rosai Hospital Spinal Cord Injury Center (K.S.), Bibai, Hokkaido; Senboku Kumiai General Hospital (S.G.), Daisen, Akita, Japan; Pfizer Japan (T.K., M.S.), Shibuya-ku, Tokyo; UBC Scientific Solutions (M.S.), Southport, CT; and Pfizer Inc. (J.M.S., L.E.K.), Groton, CT.

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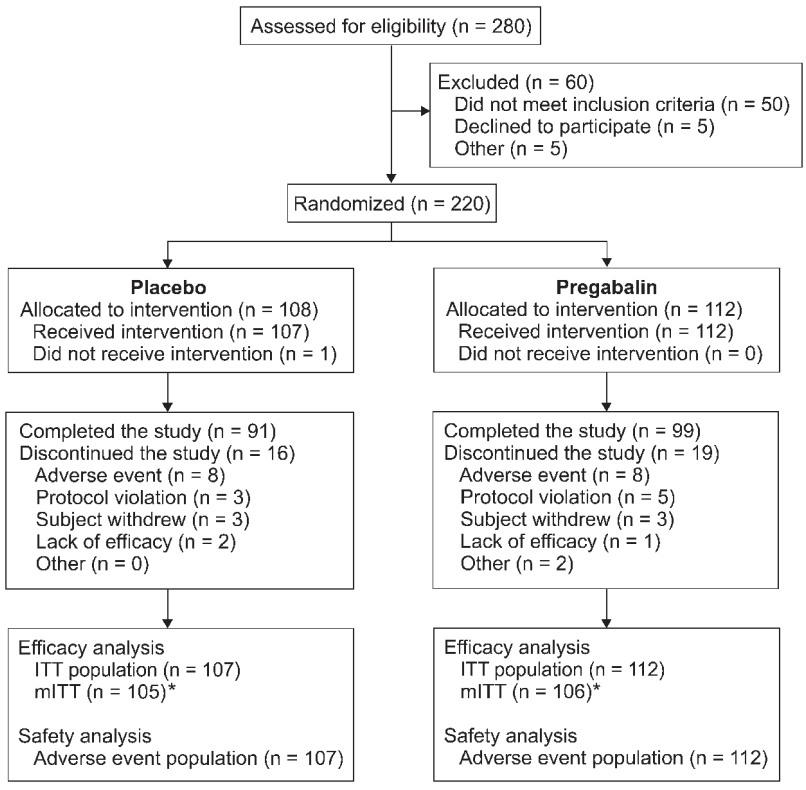
States.[13] A previous Australian-based trial demonstrated efficacy for pregabalin in the treatment of central neuropathic pain associated with traumatic SCI.[14]

The purpose of the current study was to confirm the efficacy, tolerability, and safety of pregabalin in patients with chronic central neuropathic pain due to SCI. This study builds on the previous study by including a broader (traumatic and nontraumatic SCI), larger (220 vs 137 patients), multinational patient population. Additionally, the current study includes a longer treatment duration (16 vs 12 weeks).

## METHODS

**Study population.** Patients aged ≥18 years with C2-T12 SCI, complete or incomplete, of ≥12 months' duration were recruited through physician database and peer referral from 2007 to 2011 at 60 medical centers in Chile, China, Columbia, the Czech Republic, Hong Kong, India, Japan, the Philippines, the Russian Federation, and the United States. Pain was classified in relation to the neurologic level of injury, defined as the most caudal spinal cord segment with normal sensory and motor function,[15] as above, at, or below level. Patients were required to have below-level neuropathic pain (type 14 or 15 according to Bryce-Ragnarsson taxonomy[16]) continuously for ≥3 months or remitting/relapsing for ≥6 months. Patients with SCI due to trauma, diving, ischemia, or surgery to remove benign tumors were included. An average pain score of ≥4, on an 11-point scale, in the week before randomization was also required. Key exclusion criteria included the following: the presence of other neurologic disorders, medical conditions, or pain that could confound the assessment of neuropathic pain associated with SCI; previous participation in a trial of, or intolerance to, pregabalin; intolerance to gabapentin; preexisting myelopathy of other causes; traumatic SCI superimposed on congenital canal stenosis; and retinal abnormalities or previous treatment with retinotoxic agents.

**Figure 1** Patient disposition




* Patients randomized before the protocol amendment (see Methods for details) were excluded from the modified intent-to-treat (mITT) population.

**Standard protocol approvals, registrations, and patient consents.** This study was approved by an Institutional Review Board or Independent Ethics Committee at each investigational center, and patients provided written informed consent before participation. This study was conducted in compliance with the Declaration of Helsinki and all International Conference on Harmonization Good Clinical Practice Guidelines, and is registered on Clinicaltrials.gov (NCT00407745).

**Study design/treatment.** The study comprised a 4-week dose-optimization period, a 12-week dose-maintenance period, and a 1-week taper period. Investigators used the sponsor's interactive response technology system (via phone or internet) to screen, randomize, and assign treatment to patients in a double-blinded manner. The system provided a unique identification number for each patient at screening. At visit 2, a computer-generated sequence randomized patients to receive twice-daily pregabalin or matching placebo (1:1 ratio), and the investigator was provided a number used to identify study treatment. Both placebo and pregabalin were in the form of gray capsules. In this manner, treatment allocation was concealed from patient and investigator. Patients randomized to pregabalin initially received 150 mg/d for 7 days. Based on tolerability, the dose of pregabalin was increased to 300 mg/d on day 8, 450 mg/d on day 15, and 600 mg/d on day 22. After day 8, weekly dose adjustments were allowed until the end of the optimization period (day 29). During the 12-week maintenance period that followed, patients received their optimized dose of pregabalin with 1 single-level dose reduction allowed. Patients were tapered off of pregabalin over a 1-week period. Compliance was assessed by tablet counts at each visit, and <80% compliance was a cause for discontinuation. Patients were required to discontinue gabapentin or cannabinoids at least 7 days before screening, and pregabalin at least 60 days prior. Only 1 patient, however, had used pregabalin before the study. Nonsteroidal anti-inflammatory drugs, cyclo-oxygenase-2 inhibitors, and acetaminophen (≤1.5 g/d in Japan, ≤4 g/d in all other countries) were permitted as rescue therapy. Antidepressants were permitted if the patient was on a stable dose within 30 days before the first visit.

**Efficacy assessments.** The primary efficacy outcome was duration-adjusted average change (DAAC) in pain. DAAC is a weighted average, proportional to participation duration, of observed and unobserved (missing) pain scores. Missing pain scores are imputed with a value of 0, which assumes no change from baseline. Pain scores were derived from diaries, in which patients rated the intensity of their SCI-associated pain during the previous 24 hours on an 11-point scale from 0 = no pain to 10 = worst possible pain.

Key secondary outcomes included change in mean pain score from baseline to end point, percentage of patients with ≥30% reduction in mean pain score at end point, Patient Global Impression of Change (PGIC)[17] scores at end point, and change in mean pain-related sleep interference score from baseline to end point. Pain-related sleep interference scores were derived from diaries, in which patients rated their sleep during the previous 24 hours on an 11-point scale from 0 = pain did not interfere with sleep to 10 = pain completely interfered with sleep.

**Table 1** Patient demographics and baseline characteristics

| | Placebo (n = 108[a]) | Pregabalin (n = 111) |
|---|---|---|
| **Sex, n (%)** | | |
| Male | 92 (85.2) | 84 (75.7) |
| Female | 16 (14.8) | 27 (24.3) |
| **Age, y** | | |
| Mean (SD) | 45.6 (13.8) | 46.1 (12.7) |
| **Race, n (%)** | | |
| White | 43 (39.8) | 42 (37.8) |
| Black | 8 (7.4) | 6 (5.4) |
| Asian | 53 (49.1) | 57 (51.4) |
| Other | 4 (3.7) | 6 (5.4) |
| **Weight, kg** | | |
| Mean (SD) | 73.5 (17.8) | 69.9 (16.0) |
| **Pain score** | | |
| Mean (SD) | 6.5 (1.41) | 6.5 (1.45) |
| **Central pain** | | |
| Mean duration, mo (range) | 97.5 (3.0–497.0) | 97.8 (5.0–396.0) |
| Persistent in last 3 mo, n (%) | 92 (85.2) | 92 (82.9) |
| Relapsing-remitting over 6 mo, n (%) | 16 (14.8) | 19 (17.1) |
| **ASIA Impairment Scale,[15] n (%)[b]** | | |
| A: Complete | 57 (53.8) | 49 (46.7) |
| B: Incomplete | 10 (9.4) | 16 (15.2) |
| C: Incomplete | 7 (6.6) | 9 (8.6) |
| D: Incomplete | 32 (30.2) | 31 (29.5) |
| E: Normal[c] | 0 (0) | 0 (0) |
| **Causality of SCI, n (%)** | | |
| Gunshot | 7 (6.5) | 8 (7.2) |
| Accident (other than gunshot) | 84 (77.8) | 84 (75.7) |
| Other | 17 (15.7) | 19 (17.1) |

Abbreviations: ASIA = American Spinal Injury Association; SCI = spinal cord injury.
[a] One patient was randomized to placebo but received pregabalin. The patient is listed in the placebo group, but not in figure 1.
[b] Percentages based on the modified intent-to-treat population: placebo = 106; pregabalin = 105.
[c] Patients with an ASIA impairment score of E were excluded from the trial.

Other secondary outcomes included change from baseline in mean pain and pain-related sleep interference scores at each study week. Medical Outcomes Study–Sleep Scale (MOS-SS)[18] and Hospital Anxiety and Depression Scale[19] scores were examined at baseline and end point.

**Safety and tolerability assessment.** The safety profile of pregabalin was based on observed and reported adverse events (AEs), which were evaluated by the investigator for severity and relationship to treatment. Additional measures included clinical laboratory tests, vital signs, and 12-lead EKG.

**Statistical analysis.** Sample size calculation was based on the primary DAAC end point and key secondary pain end points. A sample size of 200 patients has ≥90% power to detect a 1-point difference in DAAC, assuming a pooled SD of 1.6, and 82% power to detect a 0.9-point difference in change in mean pain score, assuming a pooled SD of 2.2. The study enrolled 220 patients.

All efficacy analyses, unless noted otherwise, were based on the modified intent-to-treat population, which included all patients who took at least 1 dose of study medication and excluded 8 patients who were randomized before the protocol was amended on February 12, 2008. This amendment was designed to reduce dropouts and sustain efficacy and tolerability throughout the study. This resulted in a 4-week flexible-dose adjustment phase (revised from a 2-week dose-escalation phase), followed by a 12-week dose-maintenance phase with 1 permissible dose reduction (revised from a 12-week fixed-dose phase). Thus, the duration of double-blind treatment from randomization to end of taper increased from 15 to 17 weeks, and the number of treatment arms decreased from 4 to 2. The safety population included every patient who received at least 1 dose of study medication and at least 1 safety assessment.

The primary end point of DAAC is defined as: (weighted mean of all daily pain scores post-baseline − mean baseline pain score) × (total post-baseline days/planned study duration). The weighted post-baseline mean pain score was calculated using the trapezoidal method. The primary analysis comparing DAAC between treatment groups used an analysis of covariance (ANCOVA) model including treatment, baseline pain score, baseline Pain Catastrophizing Scale[20] total score, and pooled center as covariates. Significance was declared if the 2-tailed test for the difference between treatment groups was significant at the 0.05 level.

Key secondary end points were analyzed using a serial gatekeeping, multiple-testing procedure. If the primary DAAC analysis was significant, then key secondary end points were analyzed in the following order: change from baseline to end point in mean pain score (ANCOVA model), percentage of patients with ≥30% decrease in pain score at end point (logistic regression model), PGIC scores at end point (Cochran-Mantel-Haenszel model), and change from baseline to end point in mean pain-related sleep interference score (ANCOVA model). Significance was declared if the unadjusted $p$ value was significant at the 0.05 level for a particular end point and for every end point preceding it. The analysis of change in mean pain score used a modified baseline-observation-carried-forward (BOCF) approach to missing data. In this method, a strict BOCF approach was used for patients who discontinued treatment because of an AE or had no post-baseline observations, and a last-observation-carried-forward (LOCF) approach was used for all other patients. All other key secondary analyses used an LOCF approach to missing data.

Secondary analyses of changes in mean pain and pain-related sleep interference scores at each week were analyzed using a mixed-model repeated-measures model on the intent-to-treat population. All other secondary end points were analyzed using an ANCOVA model and an LOCF approach to missing data with the exception of categorical items of the MOS-SS, which used a proportional odds logistic regression model.

End point refers to week 16 (before the 1-week taper period), or early termination, for all efficacy measures.

**Study hypothesis/classification of evidence.** The primary research question was to determine the efficacy of pregabalin for the treatment of neuropathic pain due to SCI. We hypothesized that pregabalin treatment would improve duration-adjusted average change in pain relative to placebo. This study provides Class I evidence that pregabalin, 150 to 600 mg/d, is effective in reducing duration-adjusted average change in pain compared with baseline in patients with spinal cord injury over a 16-week period ($p$ = 0.003, 95% confidence interval [CI] = −0.98, −0.20).

## RESULTS

**Patients.** Two hundred twenty patients were randomized to treatment (figure 1). The majority of patients were male and of Caucasian or Asian descent. Patient demographics and baseline characteristics were

**Table 2** Summary of primary and key secondary efficacy outcomes

| Pain (duration-adjusted average change)[a] | | | Versus placebo | | |
|---|---|---|---|---|---|
| **Treatment** | **No.** | **LS mean (SE)** | **Difference** | **95% CI** | ***p* Value** |
| Placebo | 106 | −1.07 (0.15) | | | |
| Pregabalin | 105 | −1.66 (0.16) | −0.59 (0.20) | (−0.98, −0.20) | 0.003 |
| Pain (change from baseline)[a] | | | | | |
| Placebo | 106 | −1.22 (0.19) | | | |
| Pregabalin | 105 | −1.92 (0.20) | −0.70 (0.25) | (−1.20, −0.20) | 0.007 |

| Pain responders (at end point)[b] | | | Versus placebo | | |
|---|---|---|---|---|---|
| **Treatment** | **No.** | **Responders, n (%)** | **OR (95% CI)** | ***p* Value** | **NNT (95% CI)** |
| Placebo | 105 | 33 (31.4) | | | |
| Pregabalin | 105 | 48 (45.7) | 1.85 (1.03, 3.33) | 0.039 | 7 (4, 96) |

| PGIC (full scale at end point) | Placebo, n = 106 | Pregabalin, n = 105 |
|---|---|---|
| Patients, n (%)[c] | | |
| Assessed | 99 (93.4) | 100 (95.2) |
| Very much improved | 2 (2.0) | 7 (7.0) |
| Much improved | 25 (25.3) | 33 (33.0) |
| Minimally improved | 24 (24.2) | 38 (38.0) |
| No change | 40 (40.4) | 19 (19.0) |
| Minimally worse | 5 (5.1) | 2 (2.0) |
| Much worse | 3 (3.0) | 0 |
| Very much worse | 0 | 1 (1.0) |
| *p* Value vs placebo[d] | | <0.001 |

| Sleep interference (change from baseline)[e] | | | Versus placebo | | |
|---|---|---|---|---|---|
| **Treatment** | **No.** | **LS mean (SE)** | **Difference** | **95% CI** | ***p* Value** |
| Placebo | 104 | −1.02 (0.20) | | | |
| Pregabalin | 105 | −2.10 (0.21) | −1.08 (0.26) | (−1.60, −0.56) | <0.001 |

Abbreviations: CI = confidence interval; LS = least squares; NNT = number needed to treat; OR = odds ratio; PGIC = Patient Global Impression of Change; SE = standard error.
[a] Scores range from 0 = no pain to 10 = worst possible pain.
[b] Patients with a ≥30% reduction in pain score from baseline.
[c] Percentage of patients assessed was calculated using number in the denominator; all other percentages were calculated using the total number assessed in the denominator.
[d] Analyzed using the Cochran-Mantel-Haenszel test without collapsing individual categories; *p* values adjusted for pooled center.
[e] Scores range from 0 = did not interfere with sleep to 10 = completely interfered.

similar between groups (table 1). Median treatment duration in both groups was 119.0 days and 68.5% of patients received 91 to 120 days of study drug. The average daily dose of pregabalin was 409.7 mg/d during the dose-maintenance period and 357.0 mg/d over the full treatment period. Overall, 11.3%, 21.7%, 28.3%, and 38.7% of patients received a maximum daily dose of pregabalin of 150, 300, 450, and 600 mg/d, respectively. A majority of patients (90.9%) received at least 1 concomitant drug treatment during the study. Common treatments included baclofen, benzodiazepines, and opioids (table e-1 on the *Neurology*® Web site at www.neurology.org).

**Primary and key secondary efficacy measures.** In the modified intent-to-treat population, pregabalin treatment improved DAAC in pain during the 16-week treatment period compared with placebo ($p = 0.003$; table 2). Analysis of a subset of patients completing the study in a treatment-compliant manner yielded similar results. In this subset, pregabalin treatment (n = 77) resulted in a mean (95% CI) improvement of −0.69 (−1.12, −0.26) over placebo (n = 80; $p = 0.002$).

According to the predefined serial gatekeeping, multiple-testing procedure, pregabalin treatment improved all key secondary outcome measures compared with placebo (table 2). These included change in mean pain score from baseline to end point, percentage of patients achieving a ≥30% decrease in mean pain score at end point, PGIC scores (full scale) at end point, and change in mean pain-related sleep interference score from baseline to end point. The analysis of change in mean pain score from baseline to end point utilized a modified BOCF approach to missing data (see Methods). However, pregabalin treatment also resulted in a least-squares mean (standard error) improvement over placebo of −0.63 (0.25) and −0.78 (0.26) using strict BOCF ($p = 0.013$) and LOCF ($p = 0.003$) approaches to missing data, respectively.

**Other secondary efficacy measures.** Improvements over placebo for both pain and pain-related sleep interference scores were evident after 1 week of pregabalin treatment and were sustained throughout the trial ($p = 0.05$; figure e-1). The pregabalin arm had a greater percentage of patients experiencing a ≥50% decrease in pain score compared with placebo at end point (29.5% vs 15.2%; odds ratio = 2.24; $p = 0.026$; number needed to treat [95% CI] = 7 [4, 34]). Treatment with pregabalin also resulted in improvement over placebo on the Sleep Disturbance, Awaken Short of Breath, Sleep Quantity, and Optimal Sleep subscales of the MOS-SS, as well as the overall Sleep Problems Index (all $p < 0.05$; table 3). Improvements over placebo were also evident for the Depression subscale of the Hospital Anxiety and Depression Scale at end point (table 3).

**Safety measures.** Treatment-related AEs, most frequently somnolence, dizziness, edema, dry mouth, fatigue, and blurred vision, occurred more frequently with pregabalin than with placebo (table 4). The majority of AEs were mild to moderate in severity. There was 1 treatment-related serious AE of hypoglycemia that resolved upon permanent discontinuation of pregabalin treatment. Although not present in ≥5% of either treatment arm, the occurrence of weight increase as an AE was higher in the pregabalin arm (2.7%) compared with placebo (1.9%). After 16 weeks, the mean change from baseline in weight was +0.8 kg in the pregabalin arm compared with −0.4 kg for placebo. There were no other clinically

**Table 3** Summary of other secondary efficacy outcomes

| MOS-SS (change from baseline)[a] | | | Versus placebo | | |
|---|---|---|---|---|---|
| Subscale | No. | LS mean (SE) | Difference | 95% CI | *p* Value |
| Placebo | 97 | −7.33 (2.72) | | | |
| Pregabalin | 100 | −16.00 (2.31) | −8.67 (2.99) | (−14.55, −2.78) | 0.004 |
| Sleep adequacy | | | | | |
| Placebo | 97 | 4.70 (2.66) | | | |
| Pregabalin | 100 | 10.48 (2.70) | 5.78 (3.49) | (−1.11, 12.66) | 0.100 |
| Snoring | | | | | |
| Placebo | 97 | −4.87 (2.66) | | | |
| Pregabalin | 100 | 0.83 (2.70) | 5.70 (3.50) | (−1.20, 12.61) | 0.105 |
| Awaken short of breath | | | | | |
| Placebo | 98 | 0.38 (1.84) | | | |
| Pregabalin | 100 | −4.76 (1.87) | −5.14 (2.42) | (−9.91, −0.37) | 0.035 |
| Sleep quantity | | | | | |
| Placebo | 98 | 0.21 (0.14) | | | |
| Pregabalin | 100 | 0.60 (0.15) | 0.38 (0.19) | (0.01, 0.76) | 0.044 |
| Somnolence | | | | | |
| Placebo | 97 | −3.22 (2.10) | | | |
| Pregabalin | 100 | −0.19 (2.14) | 3.02 (2.77) | (−2.44, 8.49) | 0.276 |
| 9-Item Sleep Problems Index | | | | | |
| Placebo | 95 | −4.83 (1.67) | | | |
| Pregabalin | 100 | −9.72 (1.68) | −4.89 (2.18) | (−9.19, −0.59) | 0.026 |

| Optimal sleep | | | Versus placebo | | |
|---|---|---|---|---|---|
| | No. | n (%) | OR | 95% CI | *p* Value |
| Placebo | 99 | 30 (30.3) | | | |
| Pregabalin | 100 | 49 (49.0) | 2.81 | (1.44, 5.49) | 0.002 |

| HADS (change from baseline)[b] | | | Versus placebo | | |
|---|---|---|---|---|---|
| Subscale | No. | LS mean (SE) | Difference | 95% CI | *p* Value |
| HADS-Anxiety | | | | | |
| Placebo | 99 | −0.82 (0.33) | | | |
| Pregabalin | 100 | −1.50 (0.34) | −0.68 (0.43) | (−1.54, 0.17) | 0.116 |
| HADS-Depression | | | | | |
| Placebo | 99 | −0.10 (0.34) | | | |
| Pregabalin | 100 | −1.09 (0.34) | −0.99 (0.45) | (−1.87, −0.11) | 0.028 |

Abbreviations: CI = confidence interval; HADS = Hospital Anxiety and Depression Scale; LS = least squares; MOS-SS = Medical Outcomes Study–Sleep Scale; OR = odds ratio; SE = standard error.
[a] Impairment is indicated by higher (sleep disturbance, snoring, awaken short of breath, somnolence) or lower (all other) scores. Scores range from 0 to 100, with the exception of sleep quantity, which is measured in hours.
[b] Scores range from 0 to 21 with higher scores indicating greater severity.

**Table 4** Incidence of most common treatment-related AEs[a]

| Event | Placebo (n = 107), n (%) | Pregabalin (n = 112), n (%) |
|---|---|---|
| Patients with ≥1 AE | 50 (46.7) | 75 (67.0) |
| Patients with ≥1 SAE | 0 | 1 (0.9) |
| Patients with ≥1 severe AE | 3 (2.8) | 3 (2.7) |
| Discontinuations due to AE | 5 (4.7) | 6 (5.4) |
| Deaths | 0 | 0 |
| Somnolence | 14 (13.1) | 37 (33.0) |
| Dizziness | 6 (5.6) | 20 (17.9) |
| Peripheral edema | 3 (2.8) | 13 (11.6) |
| Dry mouth | 3 (2.8) | 9 (8.0) |
| Fatigue | 1 (0.9) | 8 (7.1) |
| Blurred vision | 0 | 7 (6.3) |
| Edema | 1 (0.9) | 6 (5.4) |

Abbreviations: AE = adverse event; SAE = serious adverse event.
[a] Occurring in ≥5% of patients in either treatment arm.

significant findings related to laboratory tests, vital signs, EKGs, or physical examinations.

**DISCUSSION** Pregabalin treatment resulted in improvements over placebo on the primary and all key secondary efficacy measures in this multinational trial of neuropathic pain due to SCI. These findings confirm those from a previous Australian trial of pregabalin for the treatment of neuropathic pain due to traumatic SCI, in which pregabalin treatment improved pain, pain-related sleep interference, PGIC scores, and MOS-SS scores at end point.[14] In both studies, pain relief was evident after 1 week of treatment and was sustained throughout the treatment period.

A novel aspect of our study is the use of DAAC as the primary efficacy measure. DAAC was used to overcome problems inherent to LOCF and BOCF approaches to missing data. LOCF assumes that a patient's response would not change from the time of dropout to the scheduled end of the trial and may overestimate actual treatment effects. BOCF is more conservative, assuming that a patient's response would be the same at baseline and end point, but underestimates actual treatment effect. DAAC uses all observed data during the entire treatment period, in contrast to using data from a single week like LOCF or BOCF. When averaging all observed and unobserved (missing) data, DAAC uses a conservative approach to the missing data by assuming no change from baseline. Thus, DAAC is a more conservative measurement than LOCF, while taking much more observed data into consideration than LOCF and BOCF analyses. In our study, pregabalin treatment resulted in statistically significant improvements in pain compared with placebo regardless of the statistical approach used. Although overall mean pain score was improved at end point, a large proportion of patients did not achieve reduction in pain of at least 30%. This is not surprising, however,

because neuropathic pain due to SCI is often severe and difficult to treat.[21]

Treatment-related AEs in this study were consistent with the known safety profile of pregabalin. However, somnolence occurred more frequently in this study (33%) and in the previous SCI study (41%)[14] than in trials of pregabalin for the treatment of diabetic peripheral neuropathy or postherpetic neuralgia (12%–16%).[22,23] This increased frequency of somnolence could be attributable to the use of concomitant medications, specifically benzodiazepines, which add to the CNS side effects of pregabalin. Additionally, somnolence in patients with SCI may result from sleep disturbance related to spasticity, incontinence, and mood disorders that are often observed in this population. Indeed, somnolence occurred more frequently in the placebo arm (13%) in this study than what is reported for other placebo-controlled trials of pregabalin (2%–6%).[13,22,23] Overall, somnolence observed in this study was mostly mild in intensity (8 moderate and 1 severe case in pregabalin-treated patients) and discontinuations due to somnolence occurred in only 1.8% of patients receiving pregabalin.

Treatment-emergent peripheral edema was reported in 13.4% of pregabalin-treated patients in this study, which is similar to the incidence reported in the previous trial of pregabalin for SCI (10%)[14] and comparable with that reported for diabetic peripheral neuropathy (6%–16%)[22,23] and postherpetic neuralgia (approximately 12%).[22] Therefore, patients with SCI do not seem more susceptible to developing peripheral edema in response to pregabalin than patients with other neuropathic pain conditions. All cases of peripheral edema were mild to moderate in intensity, with only 1 discontinuation attributed to this particular AE.

As with all clinical trials, limitations related to study design need to be considered. Exclusion criteria, for example, limit the ability to generalize our findings to central neuropathic pain of etiologies other than SCI. Additionally, the results of this 17-week trial might not extrapolate to longer periods of treatment. Finally, patient and/or clinician assumptions concerning treatment assignment could potentially bias their assessment of treatment effect.[24]

Our study included a flexible dosing phase, allowing patient and physician to customize treatment to achieve the most appropriate balance between effectiveness and tolerability. Dose escalation was not mandatory and was based on patient tolerability. Dose reductions were permitted at various times. This more accurately represents real-world clinical settings than a fixed-dose design. Although improvements in pain were evident in some patients as early as week 1, when the dose of pregabalin was 150 mg/d, most patients required higher doses. This is reflected in the average daily doses of pregabalin during the dose-maintenance (409.7 mg/d) and full treatment (357.0 mg/d) periods. Additionally, 67% of patients received a maximum daily dose of ≥450 mg/d. The average daily dose of pregabalin during the previous Australian study was 460 mg/d.[14] This suggests that patients with SCI require relatively high doses of pregabalin for management of their neuropathic pain. Treatment with pregabalin, however, should be initiated at low doses, and dose escalation should be based on both efficacy and tolerability.

Overall, our findings make pregabalin an attractive therapeutic option for the treatment of SCI-related pain, because many current options are limited by a lack of clinical trial data to support their use, a lack of efficacy, or the presence of severe side effects.[5,6]

## AUTHOR CONTRIBUTIONS

D.D. Cardenas, E.C. Nieshoff, L. Sanin: drafting/revising the manuscript for content; analysis or interpretation of data; patient recruitment; study concept or design; study supervision or coordination. K. Suda, S. Goto: drafting/revising the manuscript for content; analysis or interpretation of data; patient recruitment. T. Kaneko, J. Sporn: drafting/revising the manuscript for content; analysis or interpretation of data; study concept or design; study supervision or coordination. B. Parsons: drafting/revising the manuscript for content; analysis or interpretation of data; study supervision or coordination. M. Soulsby: drafting/revising the manuscript for content. R. Yang: drafting/revising the manuscript for content; analysis or interpretation of data; statistical analysis; study supervision or coordination. E. Whalen: drafting/revising the manuscript for content; analysis or interpretation of data; statistical analysis; study concept or design; study supervision or coordination. J.M. Scavone, M. Suzuki: drafting/revising the manuscript for content; analysis or interpretation of data; study supervision or coordination. L.E. Knapp: drafting/revising the manuscript for content; analysis or interpretation of data; study concept or design; study supervision or coordination.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## DISCLOSURE

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