ORIGINAL ARTICLE

Effectiveness of Tapentadol Prolonged Release (PR) Compared with Oxycodone/Naloxone PR for the Management of Severe Chronic Low Back Pain with a Neuropathic Component: A Randomized, Controlled, Open-Label, Phase 3b/4 Study

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■ **Abstract**

Objective: To evaluate the effectiveness of tapentadol prolonged release (PR) vs. oxycodone/naloxone PR in non–opioid-pretreated patients with severe chronic low back pain with a neuropathic pain component.

Methods: Eligible patients (average pain intensity [numerical rating scale-3 (NRS-3)] ≥6; painDETECT positive/unclear) were randomized to twice-daily tapentadol PR 50 mg or oxycodone/naloxone PR 10 mg/5 mg. After a 21-day titration (maximum twice-daily doses: tapentadol PR 250 mg, or oxycodone/naloxone PR 40 mg/20 mg plus oxycodone PR 10 mg), target doses were continued for 9 weeks. The primary effectiveness endpoint was the change in NRS-3 from baseline to final evaluation; the exact repeated confidence interval (RCI) for tapentadol PR minus oxycodone/naloxone PR was used to establish noninferiority (upper limit <1.3) and superiority (confirmatory analyses).

Results: For the primary effectiveness endpoint, tapentadol PR was noninferior to oxycodone/naloxone PR (97.5% RCI: [−1.820, −0.184]; $P < 0.001$). This exact RCI also yielded

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evidence of superiority for tapentadol PR vs. oxycodone/naloxone PR (significantly greater reduction in pain intensity; $P = 0.003$). Improvements (baseline to final evaluation) in painDETECT and Neuropathic Pain Symptom Inventory scores were significantly greater with tapentadol PR vs. oxycodone/naloxone PR (all $P \leq 0.005$).

Conclusions: The study was formally shown to be positive and demonstrated, in the primary effectiveness endpoint, the noninferiority for tapentadol PR vs. oxycodone/naloxone PR. The effectiveness of tapentadol PR was superior to that of oxycodone/naloxone PR by means of clinical relevance and statistical significance (confirmatory evidence of superiority). Tapentadol PR was associated with significantly greater improvements in neuropathic pain-related symptoms and global health status than oxycodone/naloxone PR and with a significantly better gastrointestinal tolerability profile. Tapentadol PR may be considered a first-line option for managing severe chronic low back pain with a neuropathic pain component. ■

Key Words: effectiveness, tapentadol prolonged release, chronic low back pain, neuropathic pain, randomized controlled trial, RCT

INTRODUCTION

Low back pain is one of the most common chronic pain conditions worldwide[1] and is frequently associated with a neuropathic pain component.[2,3] Up to 79% of patients with severe and disabling low back pain have at least a possible neuropathic component to their low back pain.[3] Chronic pain with a neuropathic component is often difficult to diagnose and manage[4,5] and may be more severe than chronic pain without a neuropathic component.[6] Although opioids are frequently used for chronic pain management, they are often associated with poor tolerability that may lead to treatment discontinuation.[7–9] Gastrointestinal side effects, such as constipation, may be particularly problematic for patients receiving long-term opioid therapy; opioid-induced constipation typically does not improve with continued treatment and may be refractory to standard treatments.[8,10] Opioid-induced bowel dysfunction is mediated by opioid binding to receptors in the gastrointestinal tract; this results in a disruption of gastrointestinal motility and mucosal secretions, and accompanying symptoms, such as constipation.[9]

One strategy that has been developed to address opioid-induced bowel dysfunction is the coadministration of opioid analgesics with an opioid antagonist, such as naloxone, which is proposed to act on the opioid receptors of the gastrointestinal tract, blocking the unwanted side effects.[11,12] A fixed-dose combination of oxycodone/naloxone prolonged release (PR) has been shown to be effective and well tolerated for the management of moderate to severe chronic low back pain,[11] with better gastrointestinal tolerability (less constipation) compared with oxycodone PR alone.[11,12]

Tapentadol is a centrally acting analgesic with 2 mechanisms of action, μ-opioid receptor (MOR) agonism and noradrenaline reuptake inhibition (NRI).[13,14] Results from preclinical studies have demonstrated synergism between both mechanisms of action with respect to efficacy,[15,16] while lack of synergy has been demonstrated for gastrointestinal side effects.[17] The NRI activity of tapentadol contributes to its action on neuropathic pain and may provide an opioid-sparing effect, maintaining analgesic efficacy while reducing the potential for side effects associated with μ-opioid agonism.[14] Tapentadol has also been shown to re-establish descending pain inhibition in patients with pain related to diabetic peripheral neuropathy, which may counteract pain chronification.[18] The effectiveness of tapentadol PR has been demonstrated for the management of severe chronic low back pain with a neuropathic pain component in recent phase 3b studies.[19,20] Tapentadol PR has also been shown to be effective for managing moderate to severe chronic osteoarthritis knee pain,[21,22] low back pain,[22,23] pain related to diabetic peripheral neuropathy,[24] and cancer pain.[25–27] In a pooled analysis of data from 3 randomized, double-blind, placebo- and active-controlled, phase 3 studies in patients with moderate to severe chronic osteoarthritis pain or low back pain, tapentadol PR (100 to 250 mg bid) provided noninferior and even superior analgesic efficacy to that of oxycodone PR (20 to 50 mg bid), with superior gastrointestinal tolerability, based on assessments of the incidences of nausea, vomiting, and constipation.[28]

A recent randomized, multicenter, parallel-arm, open-label, active-controlled, phase 3b/4 effectiveness study (ClinicalTrials.gov Identifier: NCT01838616) was designed to evaluate the effectiveness and tolerability of tapentadol PR compared with that of oxycodone/naloxone PR for the management of severe chronic low back pain with a neuropathic pain component in non–opioid-pretreated patients. That study had 2 primary endpoints: a primary effectiveness endpoint and a co-primary endpoint that evaluated changes in bowel function (based on the Patient Assessment of Constipation Symptoms [PAC-SYM] total score) with study treatment. Detailed results for the co-primary endpoint, along with tolerability, safety, and quality of

life outcomes, will be presented separately.[29] Results for the primary effectiveness endpoint, measures of neuropathic pain-related symptoms, and global measures of health status are presented here.

METHODS

The protocol, patient information sheet, and informed consent form for this study were reviewed and approved by independent ethics committees. This study was conducted according to good clinical practice guidelines, applicable local laws, and the ethical principles laid out in the Declaration of Helsinki.

Patients

This study included men and women who were ≥18 years of age with severe chronic low back pain with a neuropathic pain component. Chronic low back pain was identified in patients with diagnosed low back pain lasting ≥3 months prior to enrollment. Eligible patients had pain requiring a strong (World Health Organization [WHO] step III) analgesic, based on the investigator's assessment. At enrollment, patients who were not taking co-analgesics were required to have an average pain intensity score of ≥6 on an 11-point numerical rating scale-3 (NRS-3; recalled average pain intensity score [11-point NRS] during the last 3 days prior to the visit; 0 = "no pain" to 10 = "pain as bad as you can imagine"). Patients who were taking co-analgesics at enrollment, which must have been discontinued during the washout period prior to randomization, were required to have an average pain intensity score of ≥5 on an 11-point NRS-3. At randomization, all patients were required to have an average pain intensity score of ≥6. The neuropathic component of patients' low back pain was evaluated using the painDETECT questionnaire (possible score of 0 to 38; increasing scores indicate the increasing probability of the presence of a neuropathic pain component).[2] At enrollment, patients were required to have a score on the painDETECT questionnaire of ≥13, with scores of 13 to 18 classified as unclear and scores of 19 to 38 classified as positive. For patients taking a stable regimen of centrally acting co-analgesics, which must have been discontinued during the washout period prior to randomization, a score of ≥9 (classified as negative) was permitted at enrollment. At randomization (after washout), all patients were required to have a painDETECT score in line with a classification of positive or unclear.

Patients were not eligible for the study if their low back pain was caused by cancer and/or metastatic diseases. Patients were also not eligible for the study if they had any clinically significant disease, active systemic or local infections, or clinically significant laboratory values, or required any painful procedures (scheduled during the study) that could (in the investigator's opinion) affect effectiveness, quality of life, or safety and tolerability assessments. Patients were excluded from the study if they had a history of alcohol or drug abuse; acute intoxication with alcohol, hypnotics, centrally acting analgesics, or psychotropic active substances; or a history of allergy or hypersensitivity to tapentadol, oxycodone, naloxone, or their formulations. Patients were also excluded from the study if they had a history of seizure disorder or epilepsy; mild or moderate traumatic brain injury, stroke, transient ischemic attack, or brain neoplasm within 1 year; severe traumatic brain injury within 15 years or residual sequelae suggesting transient changes in consciousness; or severe cardiac impairment (eg, New York Heart Association class >3, myocardial infarction <6 months prior to enrollment, unstable angina pectoris, cor pulmonale). Additional exclusion criteria included the presence of concomitant autoimmune inflammatory conditions; hypothyroidism (including myxedema) or Addison's disease; severe renal impairment or a history of or current laboratory values reflecting moderately or severely impaired hepatic function; severe respiratory depression with hypoxia and/or hypercapnia, acute or severe bronchial asthma, or severe chronic obstructive pulmonary disease; known or suspected paralytic ileus, acute biliary obstruction, or acute pancreatitis; or a history of rare hereditary problems of galactose intolerance, Lapp lactase deficiency, or glucose–galactose malabsorption.

Concomitant Medications

During the study, patients who were on a stable prestudy regimen of nonsteroidal anti-inflammatory drugs (NSAIDs) or paracetamol were permitted to continue taking those medications at the same stable dose. Selective serotonin reuptake inhibitors were permitted for the treatment of uncomplicated depression if patients had been taking a stable dose for ≥30 days prior to randomization. Medications used to treat psychiatric or neurologic disorders (other than those described in the following paragraph as prohibited) were permitted if patients had been taking a stable dose for ≥3 months prior to randomization.

With the exception of NSAIDs and paracetamol (as previously described), all analgesics and co-analgesics were prohibited during the study after the washout period. WHO step II and III analgesics, except for study drug, were prohibited within 30 days prior to randomization and during the study. Laxatives and anti-emetics as prophylaxis were prohibited within 14 days prior to randomization and during the study. Monoamine oxidase inhibitors were prohibited within 14 days prior to randomization and during the study.

Study Design

This study included a 3- to 14-day washout period, a 3-week titration period, and a 9-week continuation period (Figure 1). Patients who were taking centrally acting analgesics or co-analgesics at enrollment were required to discontinue these analgesics or co-analgesics during the washout period prior to the randomization visit and the start of study treatment; the duration of the washout period was individualized depending on the type and dose of the previous co-analgesics. At the randomization visit, patients were randomized 1:1 to initial doses of tapentadol PR 50 mg bid or oxycodone/naloxone PR 10 mg/5 mg bid. During the titration period, doses could be titrated upwards in increments of tapentadol PR 50 mg bid until the minimum target of titration was reached; the maximum permitted doses were tapentadol PR 250 mg bid and oxycodone/naloxone PR 40 mg/20 mg bid plus oxycodone PR 10 mg bid. The minimum target of titration at the end of the titration period was defined as one of the following: (1) a pain intensity score (NRS-3) of ≤4 with acceptable tolerability as reported by the patient or (2) a pain intensity score of ≤5 if pain relief and tolerability were reported by the patient and investigator as satisfactory to continue in the study and the patient was on the maximum dose of tapentadol PR or oxycodone/naloxone PR (or the maximum daily dose could not be achieved because of side effects). Patients who reached the minimum target of titration were eligible to enter a 9-week continuation period, during which they continued on the same stable dose of study drug; a single titration step (up- or down-titration; for patients taking the maximum dose, only down-titration) using the same increments as during titration was permitted during the continuation period. Patients in the tapentadol PR group who did not reach the minimum target of titration by the end of the titration period were discontinued from the study. Patients in the oxycodone/naloxone PR group who did not reach the minimum target of titration by the end of the titration period because of intolerable side effects or a lack of efficacy could be switched to tapentadol PR in a pickup arm or discontinued from the study. The option to switch to the pickup arm because of a lack of tolerability or efficacy under treatment with oxycodone/naloxone PR was possible at any time during the titration and continuation periods.

Study Evaluations

Effectiveness. Patients rated their average pain intensity during the past 3 days on an 11-point NRS at each study visit or telephone call. The primary effectiveness endpoint (1 of 2 co-primary endpoints for this study) was the change in average pain intensity during the last 3 days (NRS-3) from the randomization visit (baseline) to final evaluation at the end of the continuation period or at the time of discontinuation. The second primary endpoint of the study was the change in the PAC-SYM total score from the randomization visit (baseline) to final evaluation at the end of the continuation period or at the time of discontinuation; results for that endpoint will be presented separately.

Pain intensity scores over time and changes from baseline in pain intensity scores over time were evaluated as secondary effectiveness endpoints. Pain intensity scores (11-point NRS-3) for pain radiating toward or into the leg were also evaluated as a secondary endpoint. The patient global impression of change (PGIC) and clinician global impression of change (CGIC), which were used to evaluate patients' global health status, were also evaluated as secondary effectiveness endpoints. The PGIC and CGIC were completed at the randomization visit, weekly during titration (Visits 4, 6, and 8), twice during the continuation period (Visits 9 and 10), and at the final evaluation visit. For the PGIC, which is a recommended and responsive outcome for clinical trials in pain,[30,31] patients rated their overall impression of their status using a 7-point scale (1 = "very much improved" to 7 = "very much worse"). For the CGIC,[32] investigators rated their impression of the change in patients' condition with treatment using the same 7-point scale as the PGIC.

Neuropathic Pain Outcomes. Changes in neuropathic pain symptoms, based on the painDETECT questionnaire and the Neuropathic Pain Symptom Inventory (NPSI),

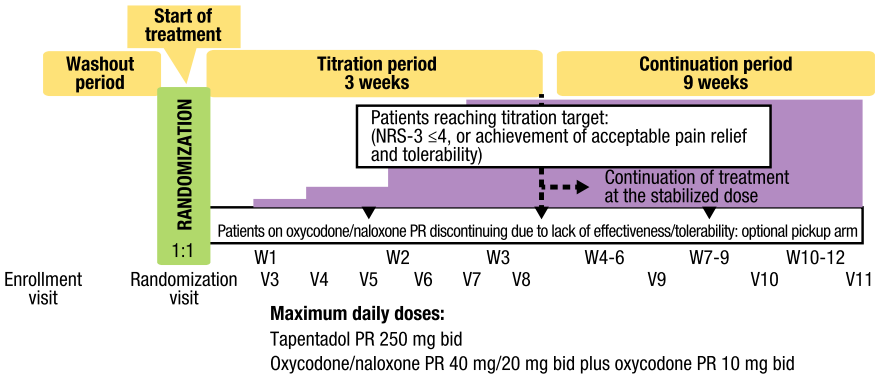

Figure 1. Study design. NRS-3, numerical rating scale-3; PR, prolonged release; W, week; V, visit; bid, twice daily.

were evaluated as secondary endpoints. The painDETECT questionnaire[2] was completed at the enrollment visit, at the randomization visit, at the end of titration (Visit 8), and at the final evaluation visit; the NPSI[33] was completed at the enrollment visit, at the randomization visit, weekly during titration (Visits 4, 6, and 8), twice during the continuation period (Visits 9 and 10), and at the final evaluation visit. The painDETECT questionnaire, which has been validated for showing the effect of treatment on neuropathic pain symptoms over time,[34] includes 7 questions addressing the frequency and quality of neuropathic pain symptoms (scored from 0 to 5; 0 = "never" to 5 = "very strongly"), 1 question addressing pain patterns over time, and 1 question evaluating radiating pain. The NPSI[33] is a validated measure that includes 10 items used to evaluate the properties of neuropathic pain; each item is scored on an 11-point NRS, with higher scores indicating more severe neuropathic pain symptoms. The NPSI[33] also includes a measure of the number of pain attacks during the previous 24 hours.

Prior to randomization to study treatment, lumbar radiculopathy was diagnosed in patients with dermatomal pain that radiated beyond the knee toward the foot and was evoked by stretching of the sciatic nerve. For a diagnosis of lumbar radiculopathy, patients were also required to have ≥1 of the following signs of root dysfunction: (1) sensory impairment, motor symptoms from compression of the lumbar nerve root; (2) absent or diminished reflexes related to affected dermatomes; and/or (3) sensory deficits in the affected painful dermatomal area, demonstrated by quantitative sensory testing.

Tolerability Outcomes and Dosing. Treatment-emergent adverse events (TEAEs) and discontinuations were monitored and recorded throughout the study. The mean daily doses of tapentadol PR and oxycodone/naloxone PR were evaluated during the titration and continuation periods.

Statistical Analyses

This study had an adaptive, 3-stage, group-sequential design (O'Brien and Fleming type design[35]); the results presented here are those of the final analysis. A 2-sample *t*-test was used for the calculation of the sample size. For both primary endpoints, a sample size of 96 patients per group in the per protocol set was required to show the noninferiority of tapentadol PR, as compared with oxycodone/naloxone PR, with 90% power and a 1-sided significance level of $\alpha = 0.0125$. Assuming that 80% of patients were available for the per protocol set, a total of 240 patients had to be allocated to study treatment. Statistical methods for the second primary endpoint (the change in the PAC-SYM total score) will be presented separately.

The safety set, which was used for the analysis of all patient characteristics and tolerability outcomes, included all randomized patients who took ≥1 dose of study drug. The full analysis set, which was used for the analysis of all secondary efficacy and quality of life endpoints, included all randomized patients who took ≥1 dose of study drug and had ≥1 postbaseline pain intensity assessment (NRS-3). The per protocol set, which was used for the analysis of the primary effectiveness endpoint, was a subpopulation of the full analysis set that included all patients who had no major protocol deviations that could impact the primary outcomes of the study.

For the primary effectiveness endpoint (the change from baseline to final evaluation in average pain intensity [NRS-3]), tapentadol PR was considered to be noninferior to oxycodone/naloxone PR if the upper limit of the 2-sided 97.5% exact repeated confidence interval (RCI) for the treatment difference (tapentadol PR

minus oxycodone/naloxone PR) was less than the noninferiority margin of 1.3. This RCI was also the basis for switching from noninferiority to superiority.[36] If the upper limit of the exact RCI was below 0, tapentadol PR also demonstrated evidence of superiority compared with oxycodone/naloxone PR in terms of statistical significance at the 1.25% level.

The main analysis for the primary efficacy endpoint (RCI) was adjusted for the group-sequential design and multiplicity, guaranteeing overall control of type I error rate (2.5% 1-sided). Confirmatory *P* values for noninferiority and superiority, based on the inverse normal method, have been determined, thus adjusting for the group-sequential design. Because there were 2 co-primary endpoints, these *P* values must be compared to the 1-sided significance level of 1.25%. Further analyses of the primary endpoints were exploratory and were not adjusted for multiplicity. As a sensitivity analysis to demonstrate the robustness of the results of the primary endpoints, the primary analyses were repeated using the full analysis set.

All other outcomes presented here are for secondary endpoints, and the respective analyses were exploratory and not adjusted for multiplicity. For the painDETECT questionnaire, scores for the 9 individual questions were summed to yield a total painDETECT score (possible score, 0 to 38). For the NPSI, scores for the 10 individual items evaluating the properties of neuropathic pain were averaged and divided by 10 to yield 5 subscores (each with a possible score of 0 to 1): burning pain (1 item), pressing pain (2 items), paroxysmal pain (2 items), evoked pain (3 items), and paresthesia/dysesthesia (2 items). The scores for all 10 individual items were also summed and divided by 100 to yield an overall feeling score (possible score, 0 to 1).

Between-group differences in PGIC and CGIC scores were evaluated using Fisher's exact test. An analysis of covariance (ANCOVA) model, including treatment and pooled center as factors and baseline value as a covariate, was used to evaluate painDETECT and NPSI outcomes and to obtain necessary *P* values for the primary effectiveness endpoint that was required as input for the inverse normal method. The last observation carried forward (LOCF) was used for imputing missing scores. The patients who entered the pickup arm were treated as discontinuations using the LOCF.

Pain intensity and neuropathic pain outcome results were evaluated separately for the subset of patients who switched from oxycodone/naloxone PR to tapentadol PR in the pickup arm and for the subsets of patients divided by painDETECT rating at baseline (positive or unclear). Pain intensity was also evaluated separately for a subset of patients who had a diagnosis of lumbar radiculopathy at baseline.

RESULTS

Patients

The safety set for this study included 258 patients (tapentadol PR, $n = 130$; oxycodone/naloxone PR, $n = 128$), the full analysis set included 256 patients (tapentadol PR, $n = 130$; oxycodone/naloxone PR, $n = 126$), and the per protocol set included 229 patients (tapentadol PR, $n = 117$; oxycodone/naloxone PR, $n = 112$). A total of 66.2% (86/130) of patients in the tapentadol PR group and 37.5% (48/128) of patients in the oxycodone/naloxone PR group completed study treatment. In the tapentadol PR and oxycodone/naloxone PR groups, respectively, 23.1% (30/130) and 51.6% (66/128) of patients discontinued treatment during the titration period and 33.8% (44/130) and 62.5% (80/128) of patients discontinued treatment during the overall treatment period. The most common reasons for study discontinuation during the overall treatment period were adverse events (AEs) and lack of efficacy (Figure 2). For the oxycodone/naloxone PR group, these percentages of discontinuations included patients who switched to tapentadol PR treatment in the pickup arm (titration period, $n = 43$; continuation period, $n = 7$) due to a lack of efficacy (titration period, $n = 11$; continuation period, $n = 4$) or the occurrence of TEAEs (titration period, $n = 32$; continuation period, $n = 3$). Of the 50 patients who entered the pickup arm, 70.0% (35/50) completed treatment; the reasons for discontinuation included AEs (18.0% [9/50]), a lack of efficacy (8.0% [4/50]), withdrawal by the patient (4.0% [1/50]), and technical problems (2.0% [1/50]).

Baseline and demographic characteristics were comparable between treatment groups in the safety set (Table 1). The mean age was approximately 58 years in both treatment groups, and there was a higher percentage of female than male patients in each treatment group. The majority of patients (>70%) in both treatment groups had a painDETECT positive rating at baseline. A diagnosis of lumbar radiculopathy was made at baseline for 58.5% (76/130) of patients in the tapentadol PR group and 58.6% (75/128) of patients in the oxycodone/naloxone PR group (Figure 3).

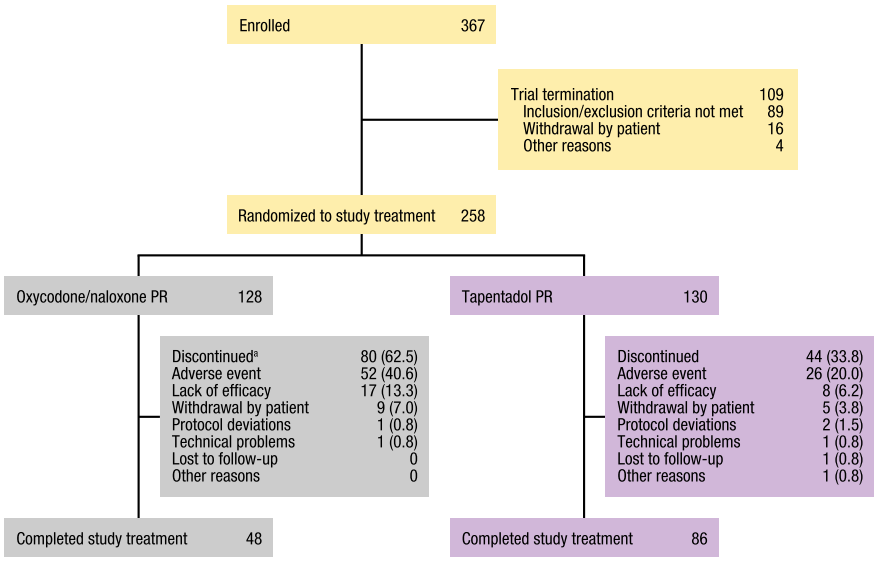

Figure 2. Patient disposition. PR, prolonged release. [a]Includes 50 patients who entered the open-label pickup arm due to a lack of efficacy (n = 15) or tolerability (n = 35).

Table 1. Demographic and Baseline Characteristics (Safety Set)

Characteristic	Oxycodone/ Naloxone PR (n = 128)	Tapentadol PR (n = 130)
Mean (SD) age, years	58.4 (12.23)	58.1 (11.48)
Gender, *n* (%)		
Female	84 (65.6)	77 (59.2)
Male	44 (34.4)	53 (40.8)
Mean (SD) BMI, kg/m^2	29.0 (5.69)	29.8 (5.55)
Race, *n* (%)		
White	128 (100)	130 (100)
Baseline painDETECT score*		
Positive	97 (75.8)	96 (73.8)
Unclear	27 (21.1)	33 (25.4)

PR, prolonged release; SD, standard deviation; BMI, body mass index.
*painDETECT ratings were not available for 1 patient in the tapentadol PR group and 4 patients in the oxycodone/naloxone PR group.

The history of patients' low back pain was generally similar in both treatment groups. On average, patients in both treatment groups had been experiencing their chronic low back pain for approximately 8 to 9 years (mean [standard deviation (SD)] duration of pain: tapentadol PR, 115.8 [121.26] months; oxycodone/naloxone PR, 102.4 [101.44] months). In the tapentadol PR and oxycodone/naloxone PR groups, respectively, the mean (SD) number of doctors that patients had visited since their pain first started was 3.5 (2.22) and 3.3 (2.14), and patients required a mean (SD) of 2.4 (2.33) and 2.5 (2.38) consultations about their pain during the previous 3 months. A total of 26.9% (35/130) of patients in the tapentadol PR group and 22.7% (29/128) of patients in the oxycodone/naloxone PR group had been hospitalized for their pain; on average, patients in both treatment groups had been hospitalized twice for their pain (mean [SD] number of hospitalizations: 2.0 [1.09] and 2.2 [2.18], respectively). The mean (SD) number of analgesic regimens that patients had taken since their pain started was 3.3 (2.50) in the tapentadol PR group and 3.3 (2.25) in the oxycodone/naloxone PR group.

During the titration period, mean (SD) daily doses were 259.0 (80.05) mg/day in the tapentadol PR group and 45.0 (18.33) mg/day in the oxycodone/naloxone PR group; during the continuation period, mean (SD) daily doses were 378.8 (129.61) and 75.3 (24.28) mg/day, respectively. The mean (SD) daily dose in the pickup arm was 301.9 (114.65) mg/day of tapentadol PR. The mean (SD) duration of exposure was 62.9 (30.84) days in the tapentadol PR group and 42.0 (34.22) days in the oxycodone/naloxone PR group. The mean (SD) duration of exposure to tapentadol PR in the pickup arm was 52.3 (24.72) days.

Effectiveness

For the primary effectiveness endpoint, tapentadol PR was noninferior to oxycodone/naloxone PR based on the exact RCI of tapentadol PR minus oxycodone/naloxone PR ([−1.820, −0.184]; $P < 0.001$ for noninferiority [inverse normal method]; confirmatory analysis). Furthermore, this exact RCI did not include 0 and therefore demonstrated evidence of the superiority of tapentadol PR vs. oxycodone/naloxone PR in terms of

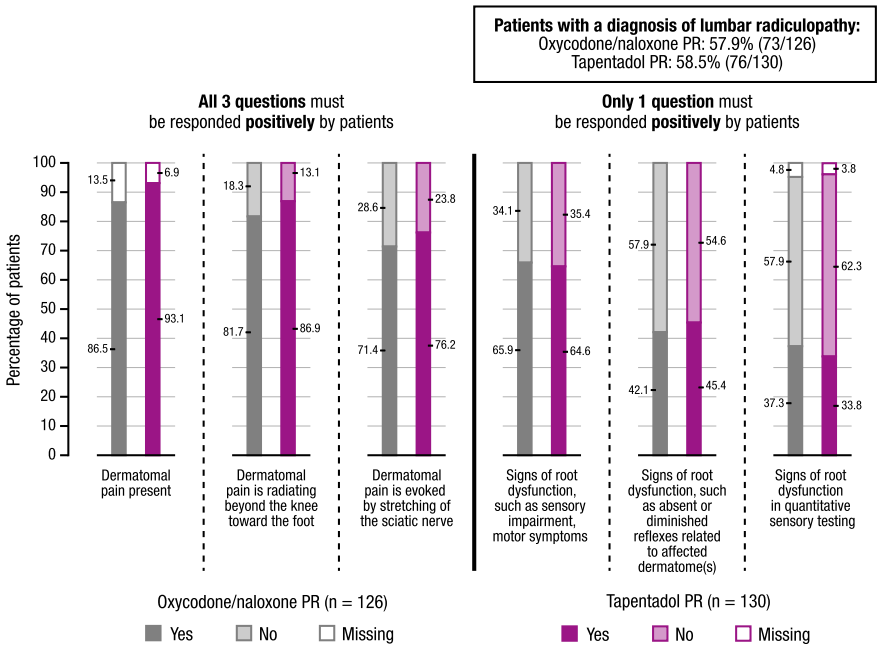

Figure 3. Diagnosis of lumbar radiculopathy (full analysis set). PR, prolonged release.

statistical significance at the 1.25% level (confirmatory analysis). The reduction in pain intensity was significantly greater with tapentadol PR than with oxycodone/naloxone PR ($P = 0.003$ for superiority; confirmatory analysis). Results of the primary endpoint were supported by a sensitivity analysis in the full analysis set using the LOCF (Table S1).

Mean pain intensity scores at baseline and final evaluation are shown in Figure 4A. Significant reductions in pain intensity from baseline to final evaluation (LOCF) were observed for both tapentadol PR and oxycodone/naloxone PR in the per protocol set (both $P < 0.001$ for the change from baseline; Figure 4B). Mean pain intensity scores over time are shown in Figure 5.

The pain intensity score for pain radiating toward or into the leg improved significantly from baseline to final evaluation in both treatment groups ($P < 0.001$; Figure 6). Improvements in pain intensity for pain radiating toward or into the leg were significantly higher in the tapentadol PR group than in the oxycodone/naloxone PR group ($P = 0.001$; Figure 6).

On the PGIC, the percentage of patients who reported a rating of "much improved" or "very much improved" was significantly higher in the tapentadol PR group (54.3% [70/129]) than in the oxycodone/naloxone PR group (29.6% [37/125]) at final evaluation ($P < 0.001$; LOCF; Figure 7A). Overall, based on PGIC results, most patients (78.5% [102/130]) in the tapentadol PR group rated their overall condition as improved. Moreover, patients in the tapentadol PR group rated their condition more favorably at final evaluation than did patients in the oxycodone/naloxone PR group ($P = 0.005$). On the CGIC, the percentage of patients for whom investigators reported a rating of "much improved" or "very much improved" was significantly higher with tapentadol PR (59.4% [76/128]) than with oxycodone/naloxone PR (35.0% [43/123]) at final evaluation ($P < 0.001$; LOCF; Figure 7B). Overall, based on CGIC results, investigators rated patients' conditions more favorably at final evaluation with tapentadol PR than with oxycodone/naloxone PR ($P = 0.005$).

Neuropathic Pain-related Symptoms

The total painDETECT score decreased significantly from baseline to final evaluation (LOCF) in both treatment groups in the full analysis set (both $P < 0.001$ for the change from baseline; Figure 8A,B). The decrease in the total painDETECT score from baseline to final evaluation was significantly greater in the tapentadol PR group than in the oxycodone/naloxone PR group (least squares [LS] mean difference [95% confidence interval (CI)], −2.9 [−4.7, −1.0]; $P = 0.002$). For all individual item scores describing symptoms of neuropathic pain on the painDETECT questionnaire, significant decreases from baseline to final evaluation (LOCF) were observed in both treatment groups of the full analysis set (all $P < 0.001$ for the change from

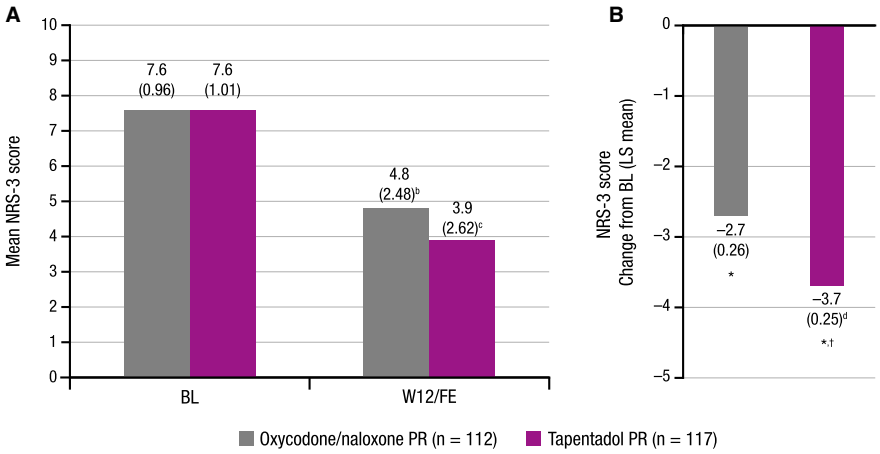

Figure 4. (A) Mean pain intensity at baseline and final evaluation and (B) change in pain intensity from baseline to final evaluation (LS mean[a]; LOCF; per protocol set). LS, least squares; LOCF, last observation carried forward; PR, prolonged release; SD, standard deviation; NRS-3, numerical rating scale-3; BL, baseline; FE, final evaluation; SEM, standard error of the mean; ANCOVA, analysis of covariance. *$P < 0.001$ for the change from baseline (exploratory analysis). †$P < 0.001$ (confirmatory analysis; noninferiority; tapentadol PR vs. oxycodone/naloxone PR); $P = 0.003$ (confirmatory analysis; superiority; tapentadol PR vs. oxycodone/naloxone PR). [a]LS means were obtained from an ANCOVA model that included treatment and pooled centers as factors and score at randomization (baseline) as a covariate. [b]Percent difference from baseline, −38.6%. [c]Percent difference from baseline, −48.7%. [d]Percent difference between tapentadol PR and oxycodone/naloxone PR, using oxycodone/naloxone PR as the base (denominator), 37.0%.

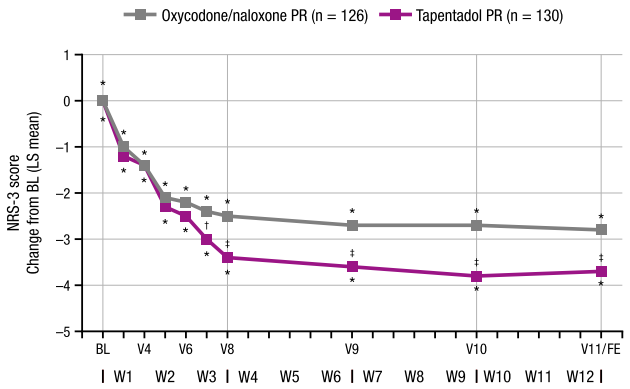

Figure 5. Changes from baseline in pain intensity scores over time (LS mean; LOCF; full analysis set).[a,b,c] LS, least squares; LOCF, last observation carried forward; PR, prolonged release; NRS-3, numerical rating scale-3; BL, baseline; V, visit; W, week; FE, final evaluation; SEM, standard error of the mean; ANCOVA, analysis of covariance. *$P < 0.001$ for the change from baseline. †$P = 0.012$ (superiority; tapentadol PR vs. oxycodone/naloxone PR). ‡$P \leq 0.002$ (superiority; tapentadol PR vs. oxycodone/naloxone PR). [a]Exploratory analyses. [b]LS means were obtained from an ANCOVA model that included treatment and pooled centers as factors and score at randomization (baseline) as a covariate. [c]SEM: oxycodone/naloxone PR, BL = 0, V3 = 0.13, V4 = 0.15, V5 = 0.18, V6 = 0.18, V7 = 0.19, V8 = 0.20, V9 = 0.23, V10 = 0.24, FE = 0.24; tapentadol PR, BL = 0, V3 = 0.12, V4 = 0.15, V5 = 0.17, V6 = 0.18, V7 = 0.19, V8 = 0.20, V9 = 0.22, V10 = 0.23, FE = 0.24.

baseline; Figure 8C). Significantly greater decreases from baseline to final evaluation were observed in the tapentadol PR group than in the oxycodone/naloxone PR group for the following individual item scores: suffering from a burning sensation in the marked area, a tingling or prickling sensation in the area of pain, light touching painful in the area (allodynia), cold or heat occasionally painful in the area (thermal pain), and slight pressure triggers pain in the area (evoked/pressure-related pain; all $P \leq 0.029$).

The NPSI overall feeling score decreased significantly from baseline to final evaluation in the tapentadol PR group (LS mean [standard error of the mean (SEM)] change from baseline to final evaluation, −0.35 [0.021]; $P < 0.001$) and in the oxycodone/naloxone PR group (−0.25 [0.021]; $P < 0.001$) of the full analysis set. The change from baseline in the overall feeling score was significantly greater in the tapentadol PR group than in the oxycodone/naloxone PR group ($P < 0.001$). Significant decreases were also observed in all NPSI subscores from baseline to final evaluation in both treatment groups of the full analysis set (all $P < 0.001$ for the change from baseline). The improvements from baseline to final evaluation in all NPSI subscores were significantly greater in the tapentadol PR group than in the oxycodone/naloxone PR group (all $P \leq 0.005$; Figure S1A). Improvements from baseline in all NPSI subscores were also significantly greater in the tapentadol PR group than in the oxycodone/naloxone PR group from Visit 8 (Week 3) until the end of the study (all $P \leq 0.012$; Figure 9A). The number of pain attacks during the previous 24 hours, as reported on the NPSI, decreased over the course of the study in both treatment groups

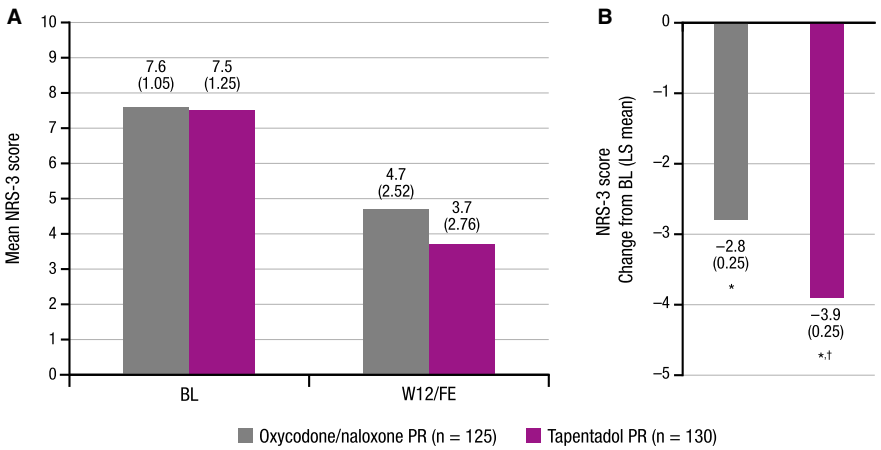

Figure 6. (A) Mean pain intensity at baseline and final evaluation and (B) change in pain intensity from baseline to final evaluation for pain radiating toward or into the leg (LS mean; LOCF; full analysis set).[a,b] LS, least squares; LOCF, last observation carried forward; SD, standard deviation; BL, baseline; FE, final evaluation; SEM, standard error of the mean; PR, prolonged release. *$P < 0.001$ for the change from baseline. †$P < 0.001$ (noninferiority; tapentadol PR vs. oxycodone/naloxone PR); $P = 0.001$ (superiority; tapentadol PR vs. oxycodone/naloxone PR). [a]Exploratory analyses. [b]LS means were obtained from an ANCOVA model that included treatment and pooled centers as factors and score at randomization (baseline) as a covariate.

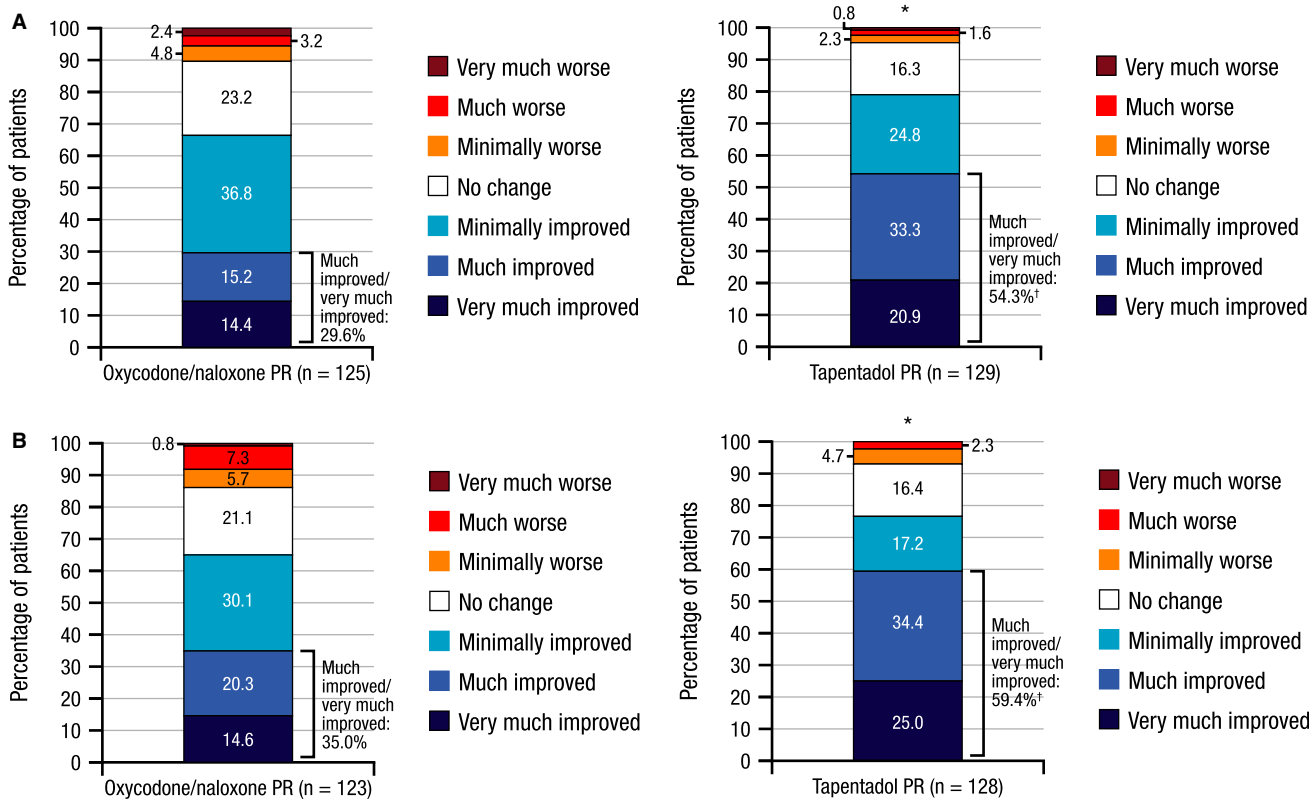

Figure 7. (A) PGIC ratings at final evaluation and (B) CGIC ratings at final evaluation (LOCF; full analysis set).[a,b,c] PGIC, patient global impression of change; CGIC, clinician global impression of change; LOCF, last observation carried forward; PR, prolonged release. *$P = 0.005$ (overall distribution of responses; superiority; tapentadol PR vs. oxycodone/naloxone PR). †$P < 0.001$ (superiority; tapentadol PR vs. oxycodone/naloxone PR). [a]Exploratory analyses. [b]*n* values are the numbers of patients with PGIC or CGIC results available for final evaluation. [c]Summary percentages for the "much improved" and "very much improved" categories may differ from the sum of those 2 percentages due to rounding.

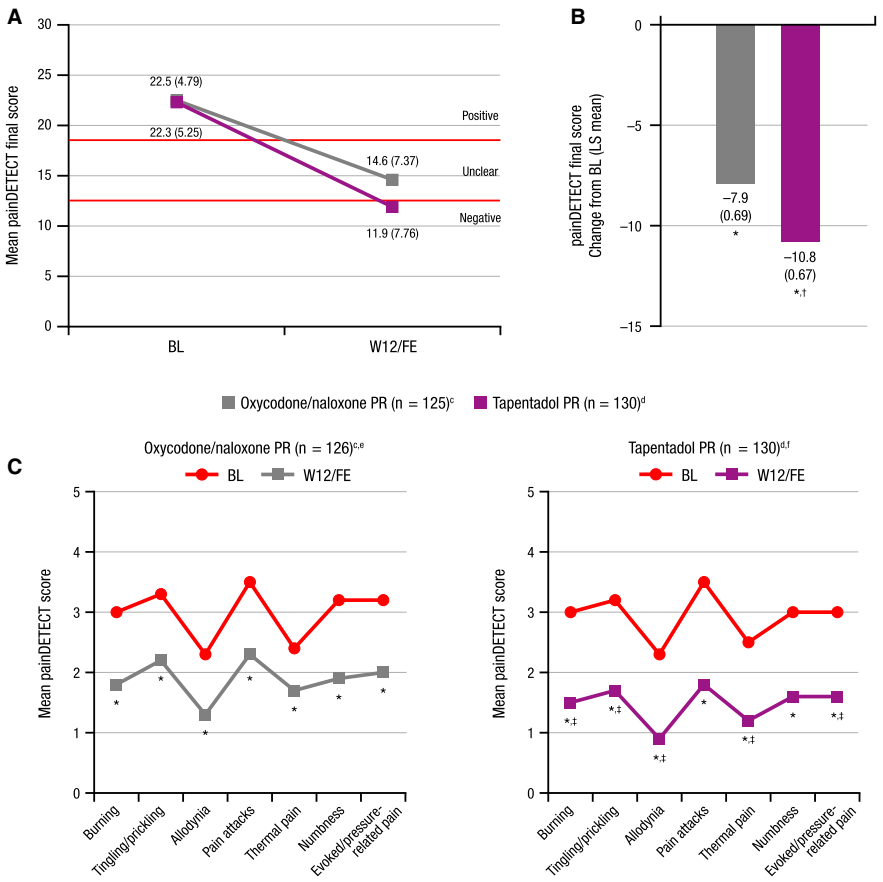

Figure 8. (A) Mean (SD) painDETECT final scores at baseline and final evaluation, (B) change in painDETECT final scores at baseline and final evaluation (LS mean), and (C) mean (SD) painDETECT individual item scores at baseline and final evaluation (LOCF; full analysis set).[a,b] SD, standard deviation; LS, least squares; LOCF, last observation carried forward; PR, prolonged release; FE, final evaluation; SEM, standard error of the mean; BL, baseline; ANCOVA, analysis of covariance. *$P < 0.001$ for the change from baseline. †$P = 0.002$ (superiority; tapentadol PR vs. oxycodone/naloxone PR). ‡$P \leq 0.029$ (superiority; tapentadol PR vs. oxycodone/naloxone PR). [a]Exploratory analyses. [b]LS means and *P* values were obtained from an ANCOVA model that included treatment and pooled centers as factors and score at randomization (baseline) as a covariate. [c]FE, $n = 115$. [d]FE, $n = 124$. [e]SD: burning, BL = 1.18, FE = 1.27; tingling/prickling, BL = 0.92, FE = 1.26; allodynia, BL = 1.35, FE = 1.31; pain attacks, BL = 1.09, FE = 1.51; thermal pain, BL = 1.33, FE = 1.43; numbness, BL = 1.08, FE = 1.33; evoked/pressure-related pain, BL = 1.18; FE = 1.49. [f]SD: burning, BL = 1.29, FE = 1.43; tingling/prickling, BL = 1.17, FE = 1.44; allodynia, BL = 1.36, FE = 1.24; pain attacks, BL = 1.20, FE = 1.64; thermal pain, BL = 1.41, FE = 1.50; numbness, BL = 1.28, FE = 1.49; evoked/pressure-related pain, BL = 1.45; FE = 1.48.

(Figure S1B). Patients generally reported fewer pain attacks in the tapentadol PR group than in the oxycodone/naloxone PR group at final evaluation ($P = 0.008$; Fisher's exact test; Figure 9B). A clear reduction in pain attacks was observed from baseline to final evaluation in both groups, but to a higher extent in the tapentadol PR group. A higher percentage of patients experienced no pain attacks during the previous 24 hours at final evaluation with tapentadol PR (31.0% [40/129]) than with oxycodone/naloxone PR (14.4% [18/125]), indicating that patients in the tapentadol PR group experienced more days without pain attacks compared with patients in the oxycodone/naloxone PR group.

Effectiveness and Neuropathic Pain-related Symptoms by Baseline painDETECT Score and Effectiveness in the Lumbar Radiculopathy Subset

Mean pain intensity scores at each visit are summarized for the full analysis set by baseline painDETECT score in Figure S2. In the full analysis set, improvements in pain intensity from baseline to final evaluation were comparable for patients with painDETECT unclear and positive ratings at baseline in both the tapentadol PR group (unclear, $n = 33$; positive, $n = 96$) and the oxycodone/naloxone PR group (unclear, $n = 27$; positive, $n = 96$). Significant decreases were observed in pain

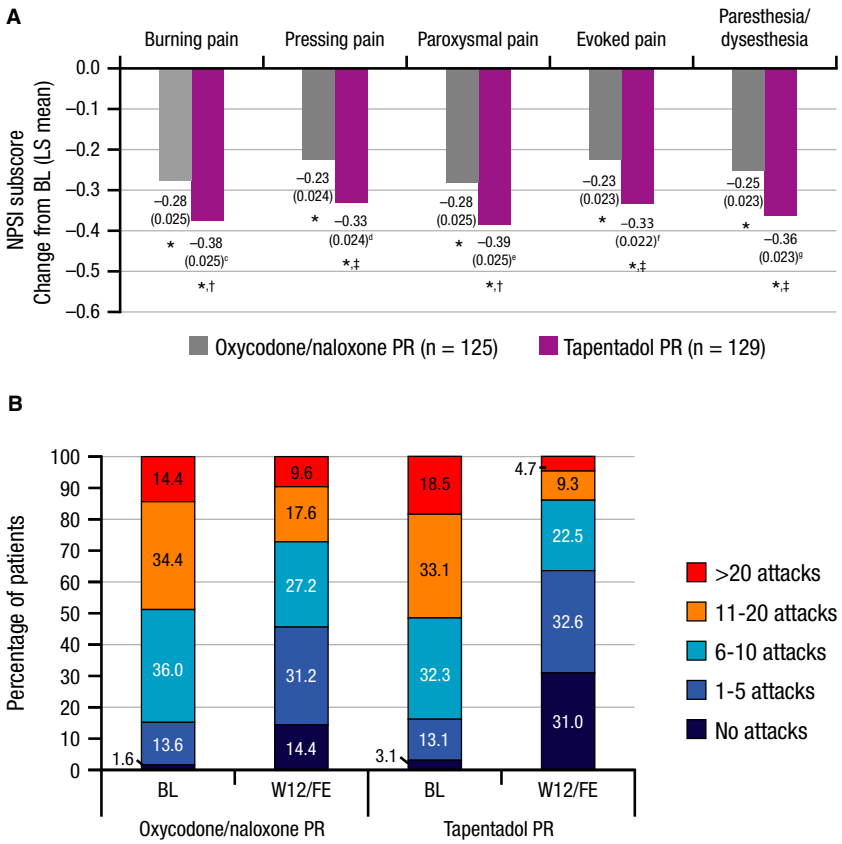

Figure 9. (A) Change from baseline to final evaluation in the NPSI subscores, and (B) number of pain attacks during the previous 24 hours as reported on the NPSI at baseline and final evaluation (full analysis set; LOCF).[a,b] NPSI, Neuropathic Pain Symptom Inventory; LOCF, last observation carried forward; LS, least-squares; PR, prolonged release; BL, baseline; FE, final evaluation; ANCOVA, analysis of covariance. *$P < 0.001$ for the change from baseline. †$P \leq 0.005$ (superiority; tapentadol PR vs oxycodone/naloxone PR). ‡$P < 0.001$ (superiority; tapentadol PR vs oxycodone/naloxone PR). [a]Exploratory analyses. [b]LS means and *P* values were obtained from an ANCOVA model that included treatment and pooled centers as factors and score at randomization (baseline) as a covariate. [c]Percent difference between tapentadol PR and oxycodone/naloxone PR, using oxycodone/naloxone PR as the base (denominator), 34.9%. [d]Percent difference between tapentadol PR and oxycodone/naloxone PR, using oxycodone/naloxone PR as the base (denominator), 46.5%. [e]Percent difference between tapentadol PR and oxycodone/naloxone PR, using oxycodone/naloxone PR as the base (denominator), 36.0%. [f]Percent difference between tapentadol PR and oxycodone/naloxone PR, using oxycodone/naloxone PR as the base (denominator), 48.4%. [g]Percent difference between tapentadol PR and oxycodone/naloxone PR, using oxycodone/naloxone PR as the base (denominator), 44.1%.

intensity scores from baseline to final evaluation (LOCF) in the tapentadol PR group (LS mean [SEM] change from baseline to final evaluation: positive, −4.0 [0.29]; unclear, −3.3 [0.54]) and in the oxycodone/naloxone PR group (positive, −3.0 [0.30]; unclear, −2.1 [0.56]; all $P < 0.001$). The reduction in pain intensity was significantly greater with tapentadol PR than with oxycodone/naloxone PR in the painDETECT positive subset (LS mean difference [97.5% CI], −1.0 [−1.9, −0.1]; $P = 0.007$ for superiority). The data showed a clear trend for greater reductions in pain intensity in the tapentadol PR group than in the oxycodone/naloxone PR group in the painDETECT unclear subset, yet the sample size was too small to reach statistical significance (LS mean difference [97.5% CI], −1.2 [−2.9, 0.6]; $P = 0.066$ for superiority).

For patients who had a diagnosis of lumbar radiculopathy at baseline (a subset of the painDETECT positive subgroup), significant improvements in pain intensity from baseline to final evaluation were observed with both tapentadol PR (LS mean [SEM] change from baseline to final evaluation, −3.5 [0.34]) and oxycodone/naloxone PR (−2.1 [0.35]; both $P < 0.001$; Figure S3). The reduction in pain intensity was significantly

Table 2. TEAEs Reported for ≥5% of Patients in Either Treatment Group During the Titration Period and the Overall Treatment Period (Safety Set)

System Organ Class, *n* (%) Preferred Term, *n* (%)	Titration Period		Overall Treatment Period	
	Oxycodone/ Naloxone PR (*n* = 128)	Tapentadol PR (*n* = 130)	Oxycodone/ Naloxone PR (*n* = 128)	Tapentadol PR (*n* = 130)
Gastrointestinal disorders	64 (50.0)	53 (40.8)	66 (51.6)	58 (44.6)
Constipation	33 (25.8)	16 (12.3)*	33 (25.8)	20 (15.4)*,†
Nausea	23 (18.0)	28 (21.5)	23 (18.0)	29 (22.3)
Vomiting	21 (16.4)	9 (6.9)*	21 (16.4)	10 (7.7)*,‡
Dry mouth	7 (5.5)	8 (6.2)	7 (5.5)	9 (6.9)
Nervous system disorders	33 (25.8)	34 (26.2)	35 (27.3)	38 (29.2)
Dizziness	22 (17.2)	22 (16.9)	22 (17.2)	24 (18.5)
Headache	5 (3.9)	9 (6.9)	5 (3.9)	10 (7.7)
General disorders and administration site conditions	32 (25.0)	40 (30.8)	35 (27.3)	40 (30.8)
Fatigue	30 (23.4)	39 (30.0)	31 (24.2)	39 (30.0)
Skin and subcutaneous tissue disorders	22 (17.2)	14 (10.8)	24 (18.8)	16 (12.3)
Hyperhidrosis	10 (7.8)	7 (5.4)	13 (10.2)	8 (6.2)
Pruritus	11 (8.6)	7 (5.4)	11 (8.6)	8 (6.2)
Infections and infestations	6 (4.7)	4 (3.1)	11 (8.6)	19 (14.6)
Nasopharyngitis	2 (1.6)	2 (1.5)	5 (3.9)	8 (6.2)

TEAE, treatment-emergent adverse event; PR, prolonged release.
*$P \leq 0.045$ vs. oxycodone/naloxone PR.
†Percent difference between tapentadol PR and oxycodone/naloxone PR, using oxycodone/naloxone PR as the base (denominator), −40.3%.
‡Percent difference between tapentadol PR and oxycodone/naloxone PR, using oxycodone/naloxone PR as the base (denominator), −53.1%.

greater with tapentadol PR than with oxycodone/naloxone PR (LS mean difference [97.5% CI], −1.3 [−2.3, −0.4]; $P = 0.001$ for superiority).

In the painDETECT positive subset, mean (SD) baseline total painDETECT scores were 24.5 (4.13) in the tapentadol PR group and 24.5 (3.22) in the oxycodone/naloxone PR group; significant decreases were observed in both treatment groups from baseline to final evaluation (LS mean [SEM] change from baseline to final evaluation, −12.4 [0.83] and −9.6 [0.84], respectively, both $P < 0.001$; Figure S4A,B). In the painDETECT unclear subset, mean (SD) baseline total painDETECT scores in the tapentadol PR and oxycodone/naloxone PR groups, respectively, were 16.2 (1.42) and 16.3 (1.41); the mean total painDETECT score decreased significantly from baseline to final evaluation in the tapentadol PR group (LS mean [SEM] change from baseline, −5.6 [1.26]; $P < 0.001$), but not in the oxycodone/naloxone PR group (−1.7 [1.37]; $P = 0.219$; Figure S4C,D). Decreases in the total painDETECT score were significantly greater in the tapentadol PR group than in the oxycodone/naloxone PR group for patients with a painDETECT positive score at baseline ($P = 0.012$) and for those with a painDETECT unclear score at baseline ($P = 0.038$). Individual item scores on the painDETECT questionnaire at baseline and final evaluation are summarized by treatment group and painDETECT rating at baseline in Figure S5. In the painDETECT positive subset, significantly greater decreases from baseline to final evaluation were observed in the tapentadol PR group than in the oxycodone/naloxone PR group of the painDETECT positive subset for the following individual item scores: suffering from a burning sensation in the marked area, a tingling or prickling sensation in the area of pain, and cold or heat occasionally painful in the area (thermal pain; all $P < 0.02$; Figure S5A). In the painDETECT unclear subset, the decrease from baseline to final evaluation was significantly greater in the tapentadol PR group than in the oxycodone/naloxone PR group for the individual item score of slight pressure triggers pain in the area (evoked/pressure-related pain; $P < 0.02$; Figure S5B).

The NPSI overall feeling score also improved significantly from baseline to final evaluation for patients with baseline painDETECT positive and unclear scores in the tapentadol PR group (both $P < 0.001$) and the oxycodone/naloxone PR group (both $P \leq 0.013$), and improvements were significantly greater in the tapentadol PR group than in the oxycodone/naloxone PR group for both painDETECT subsets ($P \leq 0.008$). Changes from baseline to final evaluation in NPSI subscores are summarized by treatment group and painDETECT rating at baseline in Figure S6.

Tolerability

In the tapentadol PR and oxycodone/naloxone PR groups of the safety set, respectively, ≥1 TEAE was reported for 66.2% (86/130) and 75.8% (97/128) of patients during the titration period and for 76.9% (100/130) and 83.6% (107/128) of patients during the overall treatment period. The overall incidence of gastrointestinal disorders was numerically lower in the tapentadol PR group than in the oxycodone/naloxone PR group during both the titration period and the overall treatment period (Table 2). The incidences of constipation and vomiting were significantly lower in the tapentadol PR group than in the oxycodone/naloxone PR group during titration and the overall treatment period (all $P \leq 0.045$).

Overall, 21.5% (28/130) of patients in the tapentadol PR group and 42.2% (54/128) of patients in the oxycodone/naloxone PR group experienced a TEAE that led to study discontinuation ($P < 0.001$ for tapentadol PR vs. oxycodone/naloxone PR). For the oxycodone/naloxone PR group, this included 35 patients who dropped into the open-label pickup arm due to TEAEs. In the tapentadol PR and oxycodone/naloxone PR groups, respectively, gastrointestinal TEAEs led to study discontinuation in 14.6% (19/130) and 21.1% (27/128) of patients, and nervous system TEAEs led to study discontinuation in 4.6% (6/130) and 17.2% (22/128) of patients ($P = 0.001$ for tapentadol PR vs. oxycodone/naloxone PR).

Effectiveness, Neuropathic Pain-related Symptoms, and Tolerability in the Pickup Arm

For 50 patients who switched from oxycodone/naloxone PR to tapentadol PR in the pickup arm, the mean (SD) pain intensity score at baseline (randomization) of the overall study was 7.6 (1.01), and the mean (SD) pain intensity score at baseline of the pickup arm was 5.8 (1.96). The mean (SD) pain intensity score was lower at all study visits and at final evaluation (4.5 [2.10]) than at baseline (randomization) of the overall study or at pickup baseline. Significant decreases in mean pain intensity were observed from baseline (randomization) to final evaluation (mean [SD] change from baseline, −3.1 [2.08]; $P < 0.001$) and from pickup baseline to final evaluation (−1.3 [2.50]; $P < 0.001$).

painDETECT scores also decreased over the course of tapentadol PR treatment in the pickup arm. For patients in the pickup arm, the mean (SD) painDETECT score was 22.1 (5.33) at baseline (randomization) of the overall study, 17.9 (7.48) at the pickup baseline, and 13.1 (6.94) at final evaluation. Significant decreases were observed in the mean painDETECT score from baseline to final evaluation (mean [SD] change from baseline, −9.0 [7.18]; $P < 0.001$) and from pickup baseline to final evaluation (−4.3 [6.92]; $P < 0.001$). Mean NPSI overall feeling score and all subscores also improved significantly from baseline of the overall study and from pickup baseline for patients in the pickup arm (all $P \leq 0.001$).

Overall, 58.0% (29/50) of patients in the pickup arm reported ≥1 TEAE. In the subset of patients who entered the pickup arm, the incidences of the most frequently reported TEAEs (incidence ≥10%) were numerically lower during treatment with tapentadol PR in the pickup arm than during prior treatment with oxycodone/naloxone PR, as follows: dizziness (12.0% [6/50] vs. 26.0% [13/50]), nausea (10.0% [5/50] vs. 24.0% [12/50]), vomiting (8.0% [4/50] vs. 22.0% [11/50]), fatigue (4.0% [2/50] vs. 20.0% [10/50]), constipation (2.0% [1/50] vs. 26.0% [13/50]), and dry mouth (0% vs. 12.0% [6/50]).

DISCUSSION

Rationale for the Trial Design and Methodology

Chronic low back pain often has a neuropathic pain component.[2,37] Results of an epidemiologic survey of 8,000 patients with low back pain indicate that a neuropathic pain component (assessed using the painDETECT questionnaire) is likely or unclear (ie, could not be excluded) in 64.7% of patients overall with chronic low back pain[2]; for patients with severe chronic low back pain, this percentage increases to 76.6%.[2] However, neuropathic pain, including low back pain with a neuropathic pain component, is often challenging to diagnose and manage[4,5]; the neuropathic pain component may be undiagnosed in many patients with low back pain. Therapeutics that affect ascending pain pathways or only a target, such as the MOR, may not fully address the neuropathic component of low back pain[38–40] because of the potential involvement of descending noradrenergic pain pathways in the modulation of neuropathic pain.[41] Furthermore, opioid analgesics may be associated with poor tolerability,[7–9] and combination therapy with an opioid and a co-analgesic may be associated with a higher incidence of side effects and related discontinuations than monotherapy.[39,42,43] Other options are needed to optimally address low back

pain because a neuropathic pain component is present in most cases.

The NRI component of the analgesic activity of tapentadol contributes to the efficacy of tapentadol for neuropathic pain, based on preclinical and clinical experience.[14,19,20,44,45] Based on these previous findings[14,19,20,44,45] and recent evidence that indicates that tapentadol restores descending pain inhibition,[18] tapentadol PR may have a preferred analgesic activity profile for the treatment of chronic low back pain for which a neuropathic pain component cannot be excluded.

This randomized, multicenter, parallel-arm, active-controlled, phase 3b/4 study was designed to evaluate the effectiveness and tolerability of tapentadol PR compared with oxycodone/naloxone PR in non–opioid-pretreated patients with severe chronic low back pain with a neuropathic pain component. This effectiveness study was designed to provide results that are meaningful in a clinical setting,[46] and an open-label design was considered appropriate. Results from previous randomized, double-blind, placebo-controlled studies have established the efficacy and tolerability of tapentadol PR across a range of chronic pain indications,[21,23–25,47] including low back pain.[23] In context, the results of this current trial are in line with the favorable outcomes observed in 3 pivotal randomized, double-blind, placebo-controlled trials in osteoarthritis and low back pain[21,23] and with the results of a preplanned, pooled analysis of those trials, in which the superiority of tapentadol PR compared with oxycodone [Correction added after initial online publication on June 12, 2015: the text "oxycodone/naloxone" was changed to "oxycodone."] PR was demonstrated for the primary efficacy endpoints, validated quality of life parameters, and gastrointestinal tolerability.[22,28] After the efficacy and tolerability of a new medication have been established in randomized, double-blind, placebo-controlled studies, the use of open-label, "real-world" or "pragmatic" effectiveness studies for further characterization and confirmation of the results observed in the blinded controlled trials is widely accepted by regulatory agencies and Health Technology Assessment Institutions, including the German Institute for Quality and Efficiency in Health Care.[48] This trial design also overcomes the limitations associated with double-blind, randomized, controlled trials, such as the use of highly selected populations and settings during development programs that are more dissimilar from clinical practice. Furthermore, results of "real-world" or "pragmatic" effectiveness randomized controlled trials (like the current study) fulfill the criteria for evidence level 1b, according to evidence-based medicine standards, including those of the Cochrane Collaboration.[49] Randomized controlled trials evaluating safety and tolerability generally have an open-label design, which is in line with regulatory guidelines. Therefore, the open-label design of this effectiveness trial was considered appropriate to evaluate noninferiority and superiority of the effectiveness and tolerability of tapentadol PR compared with that of oxycodone/naloxone PR.

This trial also included a pickup arm that allowed patients with poor effectiveness or tolerability on oxycodone/naloxone PR to switch to tapentadol PR. Offering an alternative treatment to patients with unsatisfactory treatment results related to dose-limiting AEs or a lack of efficacy under their current analgesic treatment is common practice for trying to improve treatment outcomes in a clinical setting, but only if there is a clear rationale and a chance for improvement. In this respect, tapentadol PR, with its 2 mechanisms of action (MOR agonism and NRI), has been shown to provide improved efficacy and tolerability compared with oxycodone PR (the active component of oxycodone/naloxone PR) for different types of chronic pain in large, double-blind, randomized, controlled trials[19,22,23,28] and has also been shown to provide improved tolerability and effectiveness when rotating from strong opioids to tapentadol PR in a population of opioid responders with treatment-limiting side effects.[20,50] Given the improved tolerability profile (particularly with regard to gastrointestinal AEs) of tapentadol PR compared with oxycodone PR,[19,22,23] the inclusion of a tapentadol PR "rescue" arm seemed justifiable. Tapentadol PR may offer a central μ-opioid–sparing effect, which underlies its improved gastrointestinal tolerability profile, while the addition of locally acting naloxone to oxycodone PR would only affect constipation. Furthermore, tapentadol PR may offer a different and improved treatment profile for neuropathic pain-related symptoms (based on its NRI activity); therefore, trying tapentadol PR treatment after a lack of effectiveness with oxycodone/naloxone PR is likewise justified. On the other hand, for oxycodone/naloxone PR, tolerability advantages compared with oxycodone PR have thus far only been described in opioid-pretreated and opioid-tolerant populations.[11,12] Furthermore, relevant advantages due to the addition of naloxone were not anticipated for gastrointestinal symptoms such as nausea and/or

vomiting because these symptoms are mainly triggered centrally, where naloxone would not have a relevant impact. The pickup arm did not appear to have an influence on the discontinuation rate in the oxycodone/naloxone PR group (61.5%), which was comparable to that observed with oxycodone PR (61.7%) in the pooled analysis of data from 3 large-scale, double-blind, randomized, placebo- and active-controlled, phase 3 trials.[22] Thus, results of the current trial were generally consistent with those of earlier, double-blind, randomized, controlled trials that did not include the option of a pickup arm.[21–23,28]

In a comparative clinical trial, the titration regimen must be fair and adequate in consideration of the trial setting and objectives, as was the case in the current study. The titration regimen used in this study allowed for equianalgesic dose increases, which avoided bias associated with underdosing one of the 2 compounds if unequal dose steps were used. There is some variation in the titration regimens used for patients treated with oxycodone/naloxone PR; in general, low doses (eg, 5/2.5 mg bid) are not approved as starting doses, while increments of 10/5 mg bid (as used in the current study) are in line with the United States Food and Drug Administration–approved prescribing information.[51] The use of longer titration regimens for oxycodone/naloxone PR is not uncommon, as demonstrated in a recent randomized controlled trial of oxycodone/naloxone PR that was conducted for regulatory purposes; in that study, doses were titrated in increments of 10/5 mg bid once weekly.[52] Therefore, the titration schedule used in the current study, which offered the potential for up-titration every 3 days, was considered appropriate for both compounds.

The selected study population, which included only patients who were not previously taking opioid analgesics, differed from that in previous studies of oxycodone/naloxone PR, which only showed improved tolerability compared with oxycodone PR in populations who were currently taking opioid analgesics for their pain.[11,12] The population of the current study was expected to be more susceptible to tolerability issues than an opioid-experienced population and would thereby provide the best possible basis for comparison of opioid-induced side effects.

Effectiveness and Tolerability

In this study, both tapentadol PR and oxycodone/naloxone PR provided significant reductions in pain intensity from baseline to final evaluation in non–opioid-pretreated patients with severe chronic low back pain with a neuropathic pain component. The primary effectiveness endpoint of the trial was formally shown to be positive, demonstrating noninferiority for tapentadol PR vs. oxycodone/naloxone PR for the change from baseline to final evaluation in pain intensity (11-point NRS-3). For the primary effectiveness endpoint, the effectiveness of tapentadol PR was also demonstrated to be superior to that of oxycodone/naloxone PR, by means of clinical relevance and statistical significance (confirmatory evidence of superiority). Points to consider when switching from noninferiority to superiority in clinical trials were accounted for in this analysis.[36] Overall, tapentadol PR was associated with 37% more pain reduction than oxycodone/naloxone PR (with the percent difference between tapentadol PR and oxycodone/naloxone PR calculated using oxycodone/naloxone PR as the base [denominator]) for providing strong pain relief (Figure 4). Results of the PGIC, which is considered a key outcome in chronic pain clinical trials,[30] support these effectiveness outcomes.

Both tapentadol PR and oxycodone/naloxone PR were associated with significant improvements in neuropathic pain-related symptoms from baseline to final evaluation, based on changes in the painDETECT and NPSI questionnaires. Tapentadol PR provides better control of neuropathic pain-related symptoms than oxycodone/naloxone PR. Tapentadol PR showed a significantly greater reduction in neuropathic pain-related symptoms than oxycodone/naloxone PR, based on significantly greater improvements from baseline to final evaluation in the painDETECT final score, and the NPSI overall feeling score and all subscores. Furthermore, the percentage of patients experiencing no pain attacks at final evaluation was higher in the tapentadol PR group than in the oxycodone/naloxone PR group.

Tapentadol PR was generally well tolerated and was associated with significantly less constipation and vomiting than oxycodone/naloxone PR during both the titration period and the overall treatment period. Tapentadol was associated with approximately 40% less constipation (with the percent difference between tapentadol PR and oxycodone/naloxone PR calculated using oxycodone/naloxone PR as the base [denominator]) during the overall treatment period (Table 2). As presented separately, for the co-primary endpoint, tapentadol PR was shown to be noninferior to oxyco-

done/naloxone PR for the change in the PAC-SYM total score from baseline to final evaluation.[29]

Effectiveness by Baseline painDETECT Score and in the Lumbar Radiculopathy Subset

Minor differences were observed in results for the subsets of patients divided by baseline painDETECT score (positive or unclear). Similar significant improvements from baseline to final evaluation were observed in pain intensity scores in the painDETECT positive and unclear subsets and for patients with a lumbar radiculopathy diagnosis at baseline; the reduction in pain intensity was significantly greater with tapentadol PR than with oxycodone/naloxone PR in the painDETECT positive subset and for patients with a lumbar radiculopathy diagnosis at baseline. Although the LS mean difference showed an even greater difference between the tapentadol PR and oxycodone/naloxone PR groups in the painDETECT unclear subset than the painDETECT positive subset; the difference did not reach statistical significance, considering the small sample size. In both baseline painDETECT subsets, tapentadol PR was associated with significantly greater improvements from baseline to final evaluation in the total painDETECT score, overall NPSI score, and all NPSI subscores than oxycodone/naloxone PR.

Effectiveness and Tolerability in the Pickup Arm

Results from the pickup arm showed that patients in this study who discontinued treatment with oxycodone/naloxone PR due to poor effectiveness or tolerability experienced improvements in pain intensity, neuropathic pain-related symptoms, and tolerability after switching to tapentadol PR treatment in the pickup arm. Tolerability comparisons are based on the total incidences of these TEAEs during prior study treatment with oxycodone/naloxone PR and during treatment with tapentadol PR in the pickup arm; it is possible that some of the TEAEs reported during oxycodone/naloxone PR treatment may have resolved prior to entering the pickup arm. Therefore, pretreatment with oxycodone/naloxone PR and the method of recording AEs should be taken into account when interpreting these results. Still, these results support those of a previous phase 3b study that showed that patients with severe chronic low back pain who rotated directly from WHO step III opioids to tapentadol PR experienced statistically significant improvements in pain intensity and neuropathic pain-related symptoms, despite the fact that their pain was well controlled at baseline with their prior analgesic regimen; 62.4% of patients in that study had at least a possible neuropathic component (painDETECT unclear or positive score at baseline) to their low back pain.[20]

Dosing Ratio and Superiority

Mean doses of tapentadol PR and oxycodone/naloxone PR in the current study were in line with the 5:1 equianalgesic ratio established for tapentadol PR vs. oxycodone PR in earlier randomized controlled studies;[21,23] however, tapentadol PR was associated with superior analgesic effectiveness to that of oxycodone/naloxone PR. These results also support previous evidence from the pooled analysis of data from 3 randomized, double-blind, placebo- and active-controlled, phase 3 studies in patients with moderate to severe chronic osteoarthritis pain or low back pain; results of that analysis showed that tapentadol PR (100 to 250 mg bid) provided noninferior and even superior analgesic efficacy to that of oxycodone PR (20 to 50 mg bid), with superior gastrointestinal tolerability at a 5:1 ratio of mean modal daily doses after dose stabilization.[28]

CONCLUSIONS

In this study, both tapentadol PR and oxycodone/naloxone PR provided significant reductions in pain intensity from baseline to final evaluation in non–opioid-pretreated patients with severe chronic low back pain with a neuropathic pain component. The primary effectiveness endpoint of the study was formally shown to be positive, demonstrating noninferiority for tapentadol PR vs. oxycodone/naloxone PR. The effectiveness of tapentadol PR was shown to be superior to that of oxycodone/naloxone PR by means of clinical relevance and statistical significance (confirmatory evidence of superiority). Both study treatments were associated with significant reductions in neuropathic pain-related symptoms, and these improvements were significantly greater with tapentadol PR than with oxycodone/naloxone PR. In general, there were significantly better overall outcomes for PGIC and CGIC with tapentadol PR vs. oxycodone/naloxone PR, with a significantly greater

percentage of patients and investigators, respectively, reporting ratings of "much improved" or "very much improved." Tapentadol PR was generally safe and well tolerated, with a significantly better gastrointestinal tolerability profile. Overall, these results show that tapentadol PR is effective in managing severe chronic low back pain and is superior to oxycodone/naloxone PR in providing strong pain relief. Based on these study results, tapentadol PR may be considered a first-line option for managing severe chronic low back pain with a neuropathic pain component.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Figure S1. (A) Change from baseline to final evaluation in the NPSI overall feeling score, and (B) mean NPSI subscores over time (full analysis set; LOCF).[a,b]

Figure S2. (A) Mean pain intensity at baseline and final evaluation in the painDETECT positive subset, (B) change in pain intensity from baseline to final evaluation in the painDETECT positive subset, (C) mean pain intensity at baseline and final evaluation in the painDETECT unclear subset, and (D) change in pain intensity from baseline to final evaluation in the painDETECT unclear subset (LOCF; full analysis set).[a,b]

Figure S3. (A) Mean pain intensity at baseline and final evaluation and (B) change in pain intensity from baseline to final evaluation in the lumbar radiculopathy subset (LOCF; full analysis set).[a,b]

Figure S4. (A) Mean (SD) painDETECT final scores at baseline and final evaluation in the painDETECT positive subset, (B) change in painDETECT final scores at baseline and final evaluation (LS mean [SEM]) in the painDETECT positive subset, (C) mean (SD) painDETECT final scores at baseline and final evaluation in the painDETECT unclear subset, (D) change in painDETECT final scores at baseline and final evaluation (LS mean [SEM]) in the painDETECT unclear subset (LOCF; full analysis set).[a,b]

Figure S5. Mean (SD) painDETECT individual item scores at baseline and final evaluation for the (A) painDETECT positive subset and (B) painDETECT unclear subset (LOCF; full analysis set).[a,b]

Figure S6. (A) Change from baseline to final evaluation in the NPSI subscores in the painDETECT positive subset and (B) change from baseline to final evaluation in the NPSI subscores in the painDETECT unclear subset (full analysis set; LOCF).[a,b]

Table S1. Mean pain intensity (NRS-3) scores and changes in mean pain intensity (LOCF; full analysis set).

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