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## ORIGINAL ARTICLE

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# Effectiveness and Safety of Tapentadol Prolonged Release (PR) Versus a Combination of Tapentadol PR and Pregabalin for the Management of Severe, Chronic Low Back Pain With a Neuropathic Component: A Randomized, Double-blind, Phase 3b Study

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Ralf Baron, MD, PhD<sup>\*</sup>; Emilio Martin-Mola, MD, PhD<sup>†</sup>; Matthias Müller, MD, MSc<sup>‡</sup>; Cecile Dubois, MS<sup>§</sup>; Dietmar Falke, PhD<sup>‡</sup>; Ilona Steigerwald, MD<sup>‡</sup>

*<sup>\*</sup>Division of Neurological Pain Research and Therapy, Department of Neurology, University Hospital, Schleswig-Holstein Campus Kiel, Kiel, Germany; <sup>†</sup>Department of Rheumatology, University Hospital La Paz, Autonomous University of Madrid, Madrid, Spain; <sup>‡</sup>Medical Affairs Europe & Australia, Grünenthal GmbH, Aachen, Germany; <sup>§</sup>Global Biometrics in Grünenthal Innovation, Grünenthal GmbH, Aachen, Germany*

Address correspondence and reprint requests to: Ilona Steigerwald, MD, Grünenthal GmbH, Zieglerstrasse 6, 52078 Aachen, Germany. E-mail: [ilona.steigerwald@grunenthal.com](mailto:ilona.steigerwald@grunenthal.com).

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### ■ Abstract

**Objective:** To evaluate the effectiveness and tolerability of tapentadol PR monotherapy versus tapentadol PR/pregabalin combination therapy for severe, chronic low back pain with a neuropathic component.

**Methods:** Eligible patients had painDETECT "unclear" or "positive" ratings and average pain intensity  $\geq 6$  (11-point NRS-3 [average 3-day pain intensity]) at baseline. Patients were titrated to tapentadol PR 300 mg/day over 3 weeks. Patients with  $\geq 1$ -point decrease in pain intensity and average pain intensity  $\geq 4$  were randomized to tapentadol PR (500 mg/day) or tapentadol PR (300 mg/day)/pregabalin (300 mg/day) during an 8-week comparative period.

**Results:** In the per-protocol population ( $n = 288$ ), the effectiveness of tapentadol PR was clinically and statistically comparable to tapentadol PR/pregabalin based on the change in pain intensity from randomization to final evaluation (LOCF; LSMD [95% CI],  $-0.066 [-0.57, 0.43]$ ;  $P < 0.0001$  for noninferiority). Neuropathic pain and quality-of-life measures improved significantly in both groups. Tolerability was good in both groups, in line with prior trials in the high

dose range of 500 mg/day for tapentadol PR monotherapy, and favorable compared with historical combination trials of strong opioids and anticonvulsants for combination therapy. The incidence of the composite of dizziness and/or somnolence was significantly lower with tapentadol PR (16.9%) than tapentadol PR/pregabalin (27.0%;  $P = 0.0302$ ).

**Conclusions:** Tapentadol PR 500 mg is associated with comparable improvements in pain intensity and quality-of-life measures to tapentadol PR 300 mg/pregabalin 300 mg, with improved central nervous system tolerability, suggesting that tapentadol PR monotherapy may offer a favorable treatment option for severe low back pain with a neuropathic component. ■

**Key Words:** chronic pain, low back pain, neuropathic pain, tapentadol prolonged release, combination therapy, randomized controlled trial

## INTRODUCTION

Chronic low back pain is a common chronic pain condition<sup>1-4</sup> that often has a neuropathic pain component, which may complicate its management.<sup>5</sup> Different pain mechanisms are responsible for nociceptive and neuropathic pain components in chronic pain.<sup>6</sup> Descending noradrenergic modulation mechanisms appear to play an important role in neuropathic pain modulation.<sup>6</sup> Therefore, the use of monotherapy directed at the ascending pathways or specific individual targets (eg,  $\mu$ -opioid receptor [MOR] agonists) may not fully address the neuropathic component of low back pain.<sup>5,7,8</sup> To manage severe chronic pain with a neuropathic component, patients may be treated with a combination of strong opioids with co-analgesics (eg, anticonvulsants, antidepressants).<sup>9</sup> However, combination therapy may be associated with a higher incidence of side effects and related discontinuations.<sup>7,10,11</sup>

Tapentadol represents a new class of centrally acting analgesic with both MOR agonist and noradrenaline reuptake inhibitor (NRI) activities.<sup>12</sup> The efficacy of tapentadol prolonged release (PR) has been demonstrated in phase 3 studies in patients with moderate-to-severe, chronic cancer-related pain,<sup>13</sup> pain due to osteoarthritis of the knee,<sup>14</sup> low back pain,<sup>15</sup> and painful diabetic peripheral neuropathy.<sup>16</sup> A pooled analysis of data from three phase 3 studies of tapentadol PR (100 to 250 mg bid), compared with oxycodone HCl-controlled release (CR; 20 to 50 mg bid) for the management of moderate-to-severe, chronic osteoarthritis knee pain or low back pain, demonstrated that tapentadol PR provided noninferior analgesic efficacy compared with oxycodone CR. Tapentadol PR was also

associated with superior gastrointestinal tolerability (based on the incidences of nausea, vomiting, and constipation) and a lower incidence of discontinuations compared with oxycodone CR.<sup>17</sup> The effectiveness of tapentadol PR for managing severe, chronic osteoarthritis pain,<sup>18</sup> and severe, chronic low back pain with or without a neuropathic component<sup>19</sup> has been demonstrated in phase 3b studies.

Based on the MOR-NRI concept, which may address both nociceptive and neuropathic mechanisms of chronic pain, and previous results indicating that tapentadol PR is effective for managing chronic pain with a neuropathic component,<sup>16,19</sup> it was reasonable to examine whether tapentadol PR monotherapy could be as effective as a combination of tapentadol PR and pregabalin and to compare the tolerability profiles of both analgesic options. Pregabalin, an anticonvulsant drug that acts as an agonist of high-voltage-activated calcium channels,<sup>20</sup> is registered in Europe for the treatment of (peripheral and central) neuropathic pain and is frequently used for combination therapy for neuropathic low back pain. For these reasons, this randomized, double-blind, phase 3b study (ClinicalTrials.gov Identifier: NCT01352741) was designed to evaluate the effectiveness and tolerability of the combination of a medium dose of tapentadol PR and pregabalin versus a higher dose of tapentadol PR alone for managing severe, chronic low back pain with a neuropathic component.

## METHODS

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

### Patient Population

Using the inclusion criteria and the selection of patients during the titration period, we identified patients with severe or very severe low back pain with a neuropathic pain component; these patients were generally late-stage patients who would otherwise typically be treated with combinations of centrally acting analgesics, including strong opioids, and/or co-analgesics.

This study enrolled men and women who were  $\geq 18$  years of age with a diagnosis of chronic low back pain lasting  $\geq 3$  months prior to enrollment and requir-

ing a strong (World Health Organization [WHO] step III) analgesic, based on the investigator's assessment. Patients under regular, daily pretreatment with a WHO step I analgesic or no regular analgesic pretreatment were required to have an average pain intensity score  $\geq 6$  at the baseline visit 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"). If patients were taking regular WHO step II or III analgesics or centrally acting co-analgesics on a daily basis for  $\geq 2$  weeks prior to enrollment, they must have had an increase of  $\geq 1$  point in pain intensity (NRS-3) at the baseline visit (after washout) compared with the enrollment visit. Patients were required to have a score on the painDETECT questionnaire,<sup>21</sup> which was used to evaluate the likelihood of a neuropathic pain component to low back pain (possible score of 0 to 38), of "positive" (score of 19 to 38) or "unclear" (score of 13 to 18) at the baseline visit.

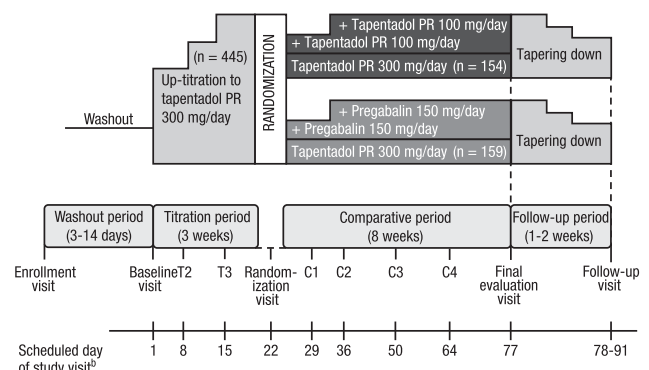
Women who were pregnant or breast-feeding could not participate in this study. Patients were excluded from the study if they had low back pain caused by cancer and/or metastatic diseases; any painful procedures (eg, major surgery) planned during the study that could affect effectiveness and safety outcomes; or other concomitant painful conditions, other than low back pain, that could confound patients' study assessments or self-evaluation of pain (eg, fibromyalgia). Additional exclusion criteria included: concomitant autoimmune inflammatory conditions; severe cardiac impairment; moderate renal impairment; a history of or current moderate or severe hepatic impairment; and other clinically significant diseases, laboratory findings, or active systemic or local infections that may affect efficacy or safety assessments. Patients were also excluded from the study if they had a history of any of the following: alcohol or drug abuse; seizure disorder or epilepsy; mild or moderate traumatic brain injury, stroke, transient ischemic attack, or brain neoplasm within 1 year of enrollment; or severe traumatic brain injury within 15 years of enrollment or residual sequelae, suggesting transient changes in consciousness. In addition, patients with a history of allergy or hypersensitivity to tapentadol, pregabalin, paracetamol, or their excipients were excluded, as were those who had contraindications and warnings related to tapentadol, pregabalin, or paracetamol that were not covered by other exclusion criteria, including acute or severe bronchial asthma, severe respiratory depression with hypoxia and/or hypercapnia, cor pulmonale, severe

chronic obstructive pulmonary disease, or nonopioid-induced paralytic ileus.

After washout, patients were not permitted to take WHO step II or III opioid analgesics and centrally acting co-analgesics during the study. Monoamine oxidase inhibitors were also prohibited within 14 days prior to enrollment and during the study. Selective serotonin reuptake inhibitors (for the treatment of uncomplicated depression) were permitted if patients were taking a stable dose for  $\geq 30$  days prior to the enrollment visit. Other medications used to treat psychiatric or neurological disorders were permitted if patients were taking a stable dose for  $\geq 3$  months prior to the enrollment visit.

### Study Design

This randomized, multicenter, multinational, double-blind, parallel-group, active-controlled phase 3b study included the following phases: an optional 3- to 14-day washout period; a 3-week open-label titration period; an 8-week double-blind comparative period; and an up to 2-week follow-up period (Figure 1). This study was conducted at 48 sites: Germany (12 sites); Poland (10 sites); Spain (8 sites); Belgium (5 sites); Austria (5 sites); Denmark (4 sites); and the Netherlands (4 sites). During the washout period (prior to starting study treatment), patients taking WHO step II or III analgesics or centrally acting co-analgesics (prescribed for low back pain) were required to discontinue those analgesics; the duration of the washout period and number of down-tapering steps



**Figure 1.** Study design.<sup>a</sup> PR, prolonged release; T, titration period; C, comparative period. <sup>a</sup>The open-label extension arm and the pickup arm are not shown in this figure. <sup>b</sup>Although the study visits were scheduled for set study days, visit timing varied from patient to patient. Visits T2, T3, and C2 could occur + 1 day as required, the randomization visit and Visit C1 could occur + 3 days as required, Visit C3 could occur  $\pm 2$  days as required, and Visit C4 (a phone contact) and the final evaluation visit could occur  $\pm 1$  day as required. The follow-up visit occurred anywhere from 1 to 2 weeks after the final evaluation visit.

depended on the type and dose of prior opioid analgesics. Patients taking WHO step I analgesics could continue on their pretreatment regimen during the washout period, but no other analgesic medication was provided; in cases of unbearable pain, the washout period could be shortened to 3 days. During the titration period, eligible patients initiated treatment with tapentadol PR 50 mg bid; doses were then titrated upwards in increments of 50 mg bid on a weekly basis until a dose of tapentadol PR 300 mg/day was reached. Interim titrations 3 days after a previous dose adjustment were permitted for patients who required more rapid up-titration. Patients were maintained on tapentadol PR 300 mg/day until the randomization visit; if pain was felt to be unbearable at that dose, patients could be referred for randomization 3 days after reaching a dose of tapentadol PR 300 mg/day.

At the randomization visit (start of the double-blind comparative period), eligible patients were randomized (1:1) to target doses of tapentadol PR 500 mg/day or tapentadol PR 300 mg/day plus pregabalin 300 mg/day. To be eligible for randomization, patients had to meet the following criteria: stable dose of tapentadol PR 300 mg/day, response to tapentadol PR ( $\geq 1$ -point reduction in pain intensity score from baseline to randomization), pain intensity score  $\geq 4$  at randomization, and no ongoing tolerability problem preventing further dose increase in tapentadol PR or the addition of pregabalin (at the discretion of the investigator). After the randomization visit, patients were titrated to tapentadol PR 300 mg/day plus tapentadol PR 100 mg/day or tapentadol PR 300 mg/day plus pregabalin 150 mg/day. One week after the randomization visit, patients were further titrated to tapentadol PR 300 mg/day plus tapentadol PR 200 mg/day or tapentadol PR 300 mg/day plus pregabalin 300 mg/day. Patients who had already reached a satisfactory level of pain relief (NRS-3  $< 4$ ), and thus did not qualify for randomization to double-blind treatment, could continue treatment on a stable dose of tapentadol PR 300 mg/day in a parallel open-label continuation arm. Patients who dropped out of the double-blind arm due to treatment-emergent adverse events (TEAEs) at least possibly related to the study drug after being randomized to double-blind treatment could continue treatment in an open-label pickup arm on lower doses of tapentadol PR (300 or 400 mg/day, depending on tolerability). Patients could take paracetamol ( $\leq 1,000$  mg/day) during the double-blind comparative period or open-label continuation arm for pain unrelated to low back pain.

Only results for the titration period and double-blind treatment arm are presented here; results for the open-label continuation arm and open-label pickup arm will be presented separately.

### Effectiveness Evaluations

At each study visit, patients rated their average pain intensity using the NRS-3. The primary end point was the change in average pain intensity (NRS-3) from randomization to the final evaluation visit (end of the comparative period). For the primary end point, a noninferiority analysis was carried out comparing the change in average pain intensity (NRS-3) from randomization to the final evaluation visit for tapentadol PR monotherapy and tapentadol PR plus pregabalin combination therapy. Pain intensity (NRS-3) values over time, the recalled worst pain intensity during the 24 hours prior to every study visit or phone call, and the pain intensity score for pain radiating toward or into the leg were evaluated as secondary end points. Additional secondary effectiveness end points included subject satisfaction with treatment, the patient global impression of change (PGIC), the clinician global impression of change (CGIC), the EuroQol-5 Dimension (EQ-5D) health status index, the Short Form-12 (SF-12) Health Survey, the Hospital Anxiety and Depression Scale (HADS), and the Sleep Evaluation Questionnaire.

The PGIC, CGIC, and subject satisfaction with treatment were evaluated on the schedule shown in Table 1. For the PGIC, patients completed the statement, "Since I began trial treatment, I would rate my overall condition as" using a 7-point rating scale (1 = "very much improved" to 7 = "very much worse"). For the CGIC, investigators responded to the question, "Compared with the patients' condition at baseline, how has it changed?" using the same scale used for the PGIC. For subject satisfaction with treatment, patients responded to the question, "How would you rate your overall satisfaction with your current pain treatment?" using a 5-point rating scale (0 = "poor" to 4 = "excellent").

### Neuropathic Pain Component Evaluations

The painDETECT questionnaire and the Neuropathic Pain Symptom Inventory (NPSI), which were completed on the schedule shown in Table 1, were used to evaluate neuropathic pain components. The painDETECT questionnaire<sup>21</sup> is a patient-reported assessment that



**Table 1. Schedule of Events**

Assessment	Enrollment	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6 + 7	Week 8 + 9	Week 10 + 11		Week 12 + 13
		Baseline	T2	T3	Randomization	C1	C2	C3	C4	Final Evaluation	Follow-up
NRS-3 (overall low back pain)	X	X	X	X	X	X	X	X	X	X	
NRS-3 (pain radiating toward/into the leg)	X	X	X	X	X	X	X	X	X	X	
NRS-3 (worst pain during the last 24 hours)	X	X	X	X	X	X	X	X	X	X	
Subject satisfaction with treatment	X	X	X	X	X	X	X	X		X	
PGIC/CGIC		X	X	X	X	X	X	X		X	
painDETECT questionnaire	X	X			X					X	
NPSI	X	X	X	X	X	X	X	X		X	
SF-12 health survey	X	X	X	X	X	X	X	X		X	
EQ-5D	X	X	X	X	X	X	X	X		X	
HADS	X	X		X	X		X			X	
Sleep Evaluation Questionnaire	X	X		X	X		X			X	

NRS-3, numerical rating scale-3; PGIC, patient global impression of change; CGIC, clinician global impression of change; NPSI, Neuropathic Pain Symptom Inventory; SF-12, Short Form-12; EQ-5D, EuroQol-5 Dimension; HADS, Hospital Anxiety and Depression Scale.

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. Scores for the 9 individual questions were summed to yield a total painDETECT score (possible score, 0 to 38). The NPSI<sup>22</sup> is a patient-rated assessment that includes 10 questions used to evaluate the properties of neuropathic pain; each item was scored on an 11-point NRS, with higher scores indicating more severe neuropathic pain symptoms. The NPSI also includes 1 question evaluating the duration of spontaneous pain and 1 question evaluating the number of pain attacks during the previous 24 hours. 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).

Patients were also evaluated for the presence of lumbar radiculopathy at baseline based on the following criteria: pain radiating beyond the knee toward the foot (sciatica), pain evoked by stretching of the sciatic nerve, and signs of root dysfunction. Signs of root dysfunction included 1 or more of the following: sensory impairment and motor symptoms from compression of the lumbo-

sacral nerve roots, absent or diminished reflexes related to the affected dermatomes (eg, quadriceps femoris or triceps surae reflexes), and sensory deficits in the affected painful dermatomal area, demonstrated by quantitative sensory testing.

### Quality-of-life and Function Evaluations

Health-related quality of life and function were evaluated using the EQ-5D health status index, the SF-12 Health Survey, the HADS, and the Sleep Evaluation Questionnaire. Patients completed these quality-of-life and function evaluations on the schedule shown in Table 1. The EQ-5D<sup>23</sup> health status questionnaire includes 5 dimensions of health-related quality of life (mobility, self-care, usual activities, pain or discomfort, and anxiety or depression), each rated on a scale from 1 (“no problems”) to 3 (“extreme problems”). The responses to each of the EQ-5D measures were scored using a utility-weighted algorithm to derive an EQ-5D health status index score between 0 and 1 (0 = “dead” to 1 = “full health”).

The SF-12 Health Survey<sup>24</sup> includes 12 questions used to evaluate 8 dimensions of functional health and well-being (physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health); each dimension was scored on a scale from 0 (“the lowest level of health”) to 100 (“the highest level of health”). For the SF-12, 2 summary scores (physical and mental health composite

scores; each with a possible score from 0 [“the lowest level of health”] to 100 [“the highest level of health”]) were calculated by combining scores from the 12 questions of the SF-12 Health Survey.

The HADS<sup>25</sup> includes 14 questions that assess different aspects of anxiety and depression; each question was answered by patients using a 4-point scale (0 to 3), with higher scores indicating more severe anxiety or depression symptoms.<sup>26</sup> For the HADS, 2 summary subscale scores (each with a possible score of 0 to 21) were calculated, 7 items were combined for an anxiety subscale score, and the remaining 7 items were combined for a depression subscale score. The Sleep Evaluation Questionnaire evaluated latency (ie, time to fall asleep), number of awakenings, time slept, and overall quality of sleep (rated as “poor,” “fair,” “good,” or “excellent”) during the previous night.

### Tolerability

Adverse events (AEs) were monitored and recorded throughout the study. TEAEs were defined as AEs that newly occurred or worsened in intensity after the first intake of study drug. TEAEs during the open-label titration period were defined as AEs that occurred on or after the first intake of study drug up to (but not including) the first intake of study drug during the double-blind or open-label continuation period. TEAEs during the comparative period were those that occurred on or after the first intake of double-blind study drug in the double-blind, comparative period up to the end of the study, discontinuation, or up to (but not including) the first intake of study drug in the open-label, pickup arm. A serious AE was defined as an AE that required hospitalization or prolongation of an existing hospitalization, resulted in persistent or significant disability or incapacity, was a congenital anomaly or birth defect, was life-threatening, resulted in death, or was considered medically important. AEs were classified according to intensity; mild AEs were those signs or symptoms that could be easily tolerated, moderate AEs were those symptoms that caused discomfort but were tolerable, and severe AEs were those symptoms that affected usual daily activity.

### Statistical Analyses

A sample size of 100 patients per group in the per-protocol population was required to provide 80% power to reject the null hypothesis for the primary

efficacy end point that tapentadol PR (500 mg/day) is inferior to a combination of tapentadol PR (300 mg/day) and pregabalin (300 mg/day), using one-sided noninferiority testing with a significance level of 2.5%, a standard deviation of 3, and a noninferiority margin of 1.2. Assuming that 70% of the patients could be included in the per-protocol population,  $\geq 143$  patients were required for each treatment group in the double-blind comparative arm. The safety set included all patients who received  $\geq 1$  dose of study drug. The full analysis set included all enrolled patients who received  $\geq 1$  dose of study drug and had  $\geq 1$  postbaseline pain intensity assessment. The safety set for the double-blind comparative arm included all patients who received  $\geq 1$  dose of study drug during the double-blind comparative period. The full analysis set for the double-blind comparative arm included all patients who received  $\geq 1$  dose of study drug during the double-blind comparative period and had  $\geq 1$  pain intensity assessment after the first intake of study drug during the double-blind comparative period. The per-protocol set was a subset of the full analysis set for the double-blind comparative period and included all randomized patients who had no major protocol deviations.

For the primary end point, the last observation carried forward (LOCF) was used for imputing missing pain intensity assessments. The primary end point was assessed using an analysis of covariance (ANCOVA) model, including treatment and center as factors and pain intensity score (NRS-3) at randomization as a covariate. The ANCOVA provided the least-squares mean estimation, as well as the treatment difference and 95% confidence interval (CI) estimates. Tapentadol PR was considered to be noninferior to tapentadol PR/pregabalin combination therapy if the upper limit of the two-sided 95% CI was  $\leq 1.2$  for the least-squares mean for treatment difference.

For all secondary end points, results presented in this article are those obtained using the LOCF for the full analysis set for the double-blind comparative arm. All secondary end points were also evaluated using observed-case analysis; results for the major secondary end points (pain intensity [NRS-3], subject satisfaction with treatment, PGIC, CGIC, NPSI, EQ-5D, SF-12, and HADS) using observed-case analysis and LOCF for the full analysis set for the double-blind comparative arm are presented in Tables S1–S7.

Between-group differences in PGIC, CGIC, and subject satisfaction with treatment results were evaluated

using a Cochran–Mantel–Haenszel test, controlling for treatment center.

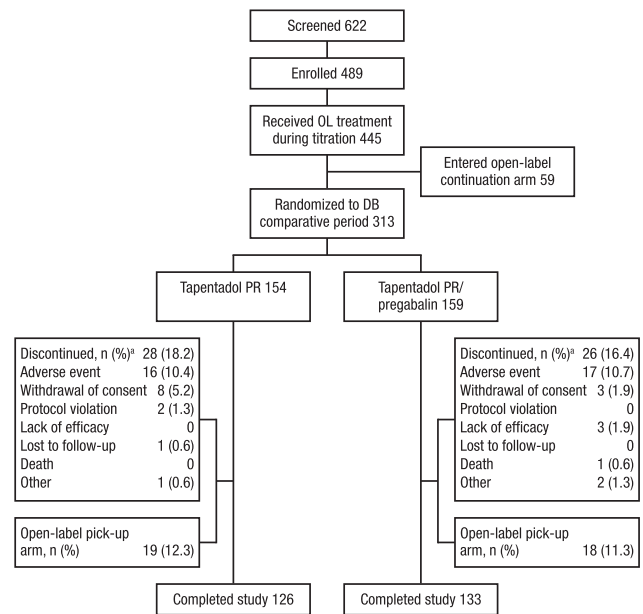
The changes from baseline to final evaluation and from randomization to final evaluation in the total painDETECT score, the HADS anxiety and depression subscale scores, the individual items of the Sleep Evaluation Questionnaire, and the NPSI subscores, and overall feeling score were evaluated using a paired *t*-test. Changes from baseline to final evaluation, and from randomization to final evaluation in the EQ-5D health status index score, and the SF-12 subscale and composite scores were evaluated using an ANCOVA model with treatment and center as effects and score at randomization as a covariate. The period from baseline to final evaluation included the open-label treatment period with tapentadol PR 300 mg, as well as the double-blind treatment period with tapentadol PR 500 mg or tapentadol PR 300 mg with pregabalin 300 mg.

## RESULTS

### Patients

Of the 622 patients who signed informed consent documents, 177 were screen failures and did not receive study medication. A total of 445 patients received study medication and were included in the safety population for the open-label phase (Figure 2). Overall, 16.4% (73/445) of patients discontinued treatment during the titration period; the reasons for discontinuation during the titration period were AEs, a lack of efficacy, withdrawal of consent, noncompliance with trial requirements, protocol violation, and other reasons. For the double-blind comparative arm, the safety set included 313 patients, the full analysis set included 309 patients, and the per-protocol set included 288 patients. A total of 59 patients from the full analysis set for the open-label phase continued taking open-label treatment in the continuation arm.

Demographic and baseline characteristics were similar between treatment groups in the safety set for the double-blind comparative arm (Table 2). At baseline, a total of 63.0% (97/154) of patients in the tapentadol PR group and 74.8% (119/159) of patients in the tapentadol PR/pregabalin group were diagnosed with lumbar radiculopathy. The history of low back pain at enrollment was relatively comparable in the tapentadol PR and tapentadol PR/pregabalin groups; the mean duration of low back pain was slightly longer in the



**Figure 2.** Patient disposition. OL, open-label; DB, double-blind; PR, prolonged release. <sup>a</sup>In the tapentadol PR group, 19 of the 28 patients who discontinued from the comparative period entered the open-label pickup arm, and in the tapentadol PR/pregabalin group, 18 of the 26 patients who discontinued from the comparative period entered the open-label pickup arm.

**Table 2. Demographic and Baseline Characteristics (Safety Set for the Double-Blind Comparative Arm)**

	Tapentadol PR 500 mg (n = 154)	Tapentadol PR 300 mg + Pregabalin 300 mg (n = 159)
Mean (SD) age, years	58.5 (11.01)	56.3 (11.83)
Gender, n (%)		
Female	95 (61.7)	86 (54.1)
Male	59 (38.3)	73 (45.9)
Mean (SD) body mass index, kg/m <sup>2</sup>	29.0 (5.50)	29.9 (5.92)
Race, n (%)		
White	154 (100.0)	158 (99.4)
Asian	0	1 (0.6)

PR, prolonged release; SD, standard deviation.

tapentadol PR group (9.4 years) than in the tapentadol PR plus pregabalin group (8.7 years; Table 3). At enrollment, the most common (incidence  $\geq 5\%$  in either treatment group) concomitant diseases and conditions, other than the study-specific pain, were hypertension (tapentadol PR, 7.1% [11/154]; tapentadol PR/pregabalin, 1.3% [2/159]), intervertebral disk protrusion (tapentadol PR, 3.9% [6/154]; tapentadol PR/pregabalin, 5.7% [9/159]), and spinal osteoarthritis (tapentadol PR, 5.2% [8/154]; tapentadol PR/pregabalin, 3.1% [5/159]).



**Table 3. History of Low Back Pain at Enrollment (Safety Set for the Double-Blind Comparative Arm)**

Parameter	Tapentadol PR 500 mg (n = 154)	Tapentadol PR 300 mg + Pregabalin 300 mg (n = 159)
Duration of pain, years		
Mean (SD)	9.4 (10.48)	8.7 (9.28)
Median (range)	5.7 (0 to 49)	6.1 (0 to 50)
Time to first pain-related consultation, months*		
Mean (SD)	9.9 (21.73)	10.7 (27.19)
Median (range)	0.9 (0 to 120)	0.6 (0 to 132)
Number of doctors visited since pain started		
Mean (SD)	4.5 (6.90)	4.3 (3.60)
Median (range)	3.0 (1 to 59)	3.0 (1 to 25)
Number of consultations within 3 months†		
Mean (SD)	3.3 (2.88)	3.5 (3.41)
Median (range)	3.0 (0 to 15)	3.0 (0 to 24)
Hospitalization due to pain, n (%)	52 (33.8)	52 (32.7)
Number of analgesic regimens offered since pain started‡		
Mean (SD)	5.0 (5.20)	4.4 (3.57)
Median (range)	4.0 (0 to 50)	3.0 (0 to 30)
Number of times taken off work due to pain per year§		
Mean (SD)	2.9 (4.50)	3.3 (5.66)
Median (range)	1.0 (0 to 24)	2.0 (0 to 37)

PR, prolonged release; SD, standard deviation.

\*Tapentadol PR 500 mg, n = 151; tapentadol PR 300 mg + pregabalin 300 mg, n = 158.

†Tapentadol PR 500 mg, n = 153; tapentadol PR 300 mg + pregabalin 300 mg, n = 158.

‡Tapentadol PR 500 mg, n = 153; tapentadol PR 300 mg + pregabalin 300 mg, n = 159.

§Tapentadol PR 500 mg, n = 39; tapentadol PR 300 mg + pregabalin 300 mg, n = 48.

Overall, 24.0% (37/154) of patients in the tapentadol PR group and 14.5% (23/159) of patients in the tapentadol PR/pregabalin group were not taking any WHO step I, II, or III analgesics or any co-analgesics at the enrollment visit. The percentages of patients taking WHO step I, II, and III analgesics or co-analgesics at enrollment and at baseline (after the washout period) are summarized in Table 4. At enrollment, antidepressants were taken as co-analgesics by 5.2% (8/154) of patients in the tapentadol PR group and by 5.0% (8/159) of patients in the tapentadol PR/pregabalin group. At randomization, nonanalgesic medications were taken by 16.9% (26/154) of patients in the tapentadol PR group and 11.3% (18/159) of patients in the tapentadol PR/pregabalin group. In particular, 1.3% (2/154) of patients in the tapentadol PR group and 0.6% (1/159) of patients in the tapentadol PR/pregabalin group were taking laxatives at randomization.

### Effectiveness

For the primary efficacy end point, the mean (standard deviation [SD]) change from randomization to final

**Table 4. Intake of WHO Step I, II, and III Analgesics and Co-Analgesics at Enrollment and Baseline (Safety Set for the Double-Blind Comparative Arm)**

Analgesic or co-analgesic, n (%)	Tapentadol PR 500 mg (n = 154)	Tapentadol PR 300 mg + Pregabalin 300 mg (n = 159)
Taken at enrollment		
WHO		
Step I	85 (55.2)	99 (62.3)
Step II	37 (24.0)	59 (37.1)
Step III	21 (13.6)	21 (13.2)
Co-analgesics	32 (20.8)	27 (17.0)
Taken at baseline		
WHO		
Step I	66 (42.9)	75 (47.2)
Step II*	2 (1.3)	3 (1.9)
Step III*	0 (0)	1 (0.3)
Co-analgesics*	8 (5.2)	3 (1.9)

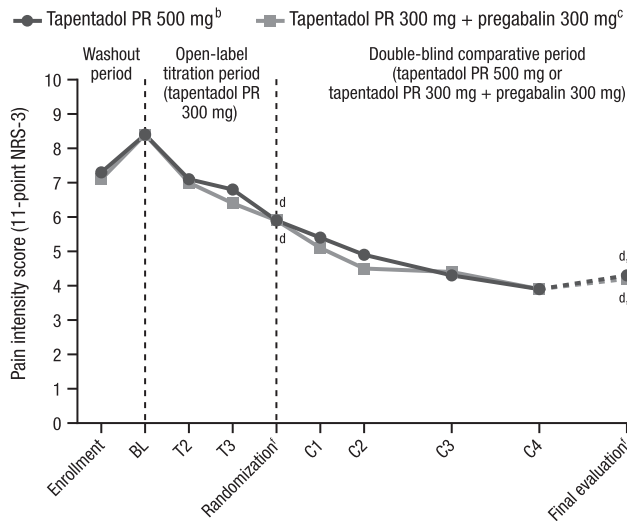
WHO, World Health Organization; PR, prolonged release.

\*Not in line with the protocol.

evaluation in pain intensity (LOCF) was  $-1.6$  (2.52) in the tapentadol PR group and  $-1.7$  (2.48) in the tapentadol PR/pregabalin group for the per-protocol set. Based on these results, the analgesic effectiveness of tapentadol PR was noninferior to that of tapentadol PR/pregabalin (least-squares mean difference [95% CI],  $-0.066$  [ $-0.57$ ,  $0.43$ ];  $P < 0.0001$  for noninferiority).

In the full analysis set for the double-blind comparative arm, the mean (SD) pain intensity score (LOCF) at baseline was  $8.4$  (1.11) in the tapentadol PR group and  $8.4$  (1.07) in the tapentadol PR/pregabalin group; mean pain intensity decreased over time (Figure 3). In the tapentadol PR and tapentadol PR/pregabalin groups, respectively, the mean (SD) changes in pain intensity from baseline to final evaluation were  $-4.1$  (2.58) and  $-4.2$  (2.66; both  $P < 0.0001$  for the change from baseline) and the mean (SD) changes in pain intensity from randomization to final evaluation were  $-1.6$  (2.47) and  $-1.7$  (2.47; both  $P < 0.0001$  for the change from randomization).

The mean (SD) pain intensity score (LOCF) for pain radiating toward or into the leg at baseline was  $8.0$  (1.82) in the tapentadol PR group and  $8.1$  (1.44) in the tapentadol PR/pregabalin group. In both treatment groups, mean pain intensity (LOCF) decreased significantly from baseline to final evaluation (mean [SD] change from baseline: tapentadol PR,  $-3.9$  [2.61]; tapentadol PR/pregabalin,  $-4.3$  [2.80]; both  $P < 0.0001$  for the change from baseline) and from randomization to final evaluation (mean [SD] change from randomization: tapentadol PR,  $-1.6$  [2.54];

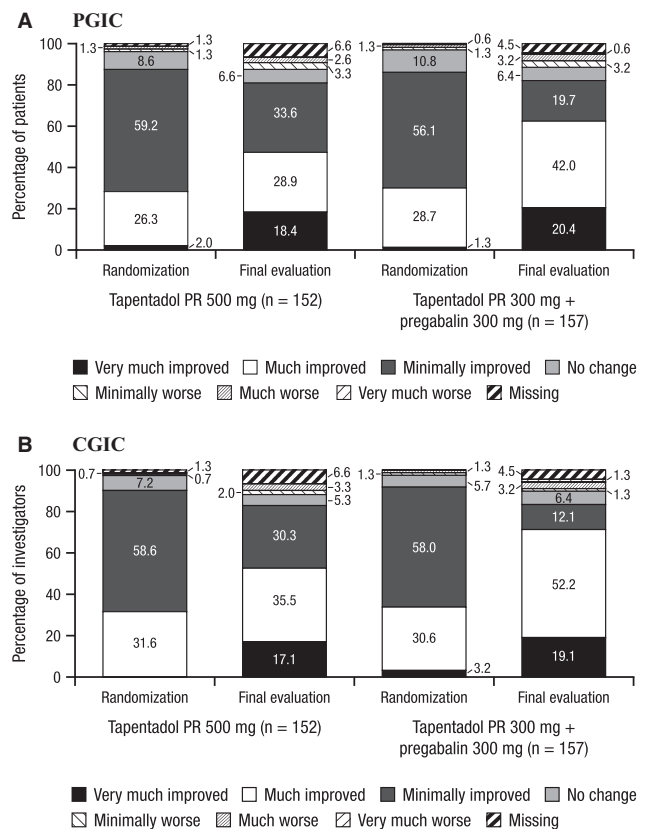


**Figure 3.** Mean pain intensity (11-point NRS-3) over time (LOCF; full analysis set for the double-blind comparative arm).<sup>a</sup> NRS-3, numerical rating scale-3; LOCF, last observation carried forward; PR, prolonged release; BL, baseline; T, titration period; C, comparative period; SD, standard deviation. <sup>a</sup>All patients received tapentadol PR 300 mg during the titration period (from baseline to randomization). <sup>b</sup>SD: enrollment, 1.24; BL, 1.11; T2, 1.68; T3, 1.69; randomization, 1.41; C1, 1.71; C2, 1.84; C3, 1.95; C4, 2.08; final evaluation, 2.56. <sup>c</sup>SD: enrollment, 1.15; BL, 1.07; T2, 1.65; T3, 1.75; randomization, 1.28; C1, 1.81; C2, 2.01; C3, 2.17; C4, 2.10; final evaluation, 2.53. <sup>d</sup> $P < 0.0001$  for the change from baseline. <sup>e</sup> $P < 0.0001$  for the change from randomization. <sup>f</sup>Pain intensity scores at randomization were the last available scores before the first intake of study drug during the double-blind comparative period, and scores at final evaluation were the last available scores after the first intake of study drug during the double-blind comparative period.

tapentadol PR/pregabalin,  $-1.9$  [2.60]; both  $P < 0.0001$  for the change from randomization). At baseline, the recalled mean (SD) worst pain intensity during the last 24 hours (LOCF) prior to assessment was  $8.4$  (1.13) in the tapentadol PR group and  $8.6$  (1.02) in the tapentadol PR/pregabalin group. The mean worst pain intensity score decreased significantly in both treatment groups from baseline to final evaluation (mean [SD] change from baseline: tapentadol PR,  $-3.8$  [2.84]; tapentadol PR/pregabalin,  $-4.1$  [2.77]; both  $P < 0.0001$  for the change from baseline) and from randomization to final evaluation (tapentadol PR,  $-1.7$  [2.66]; tapentadol PR/pregabalin,  $-1.8$  [2.56]; both  $P < 0.0001$  for the change from randomization).

The percentages of patients who reported that their satisfaction with treatment (LOCF) was “good,” “very good,” or “excellent” in the tapentadol PR and tapentadol PR/pregabalin groups, respectively, were 9.2% (14/152) and 12.1% (19/157) at baseline (prior to starting

study treatment), 55.9% (85/152) and 63.7% (100/157) at randomization, and 67.1% (102/152) and 72.6% (114/157) at final evaluation. On the PGIC (LOCF), 87.5% (133/152) of patients in the tapentadol PR group and 86.0% (135/157) of patients in the tapentadol PR/pregabalin group, respectively, reported that their overall health status was “minimally improved,” “much improved,” or “very much improved” at randomization; at final evaluation, 80.9% (123/152) and 82.2% (129/157) of patients, respectively, reported a rating of “minimally improved,” “much improved,” or “very much improved” (Figure 4A). In the tapentadol PR and tapentadol PR/pregabalin groups, respectively, a rating of “minimally improved,” “much improved,” or “very much improved” on the CGIC was reported by 90.1% (137/152) and 91.7% (144/157) of investigators at randomization and by 82.9% (126/152) and 83.4% (131/157) of investigators at final evaluation (Figure 4B).

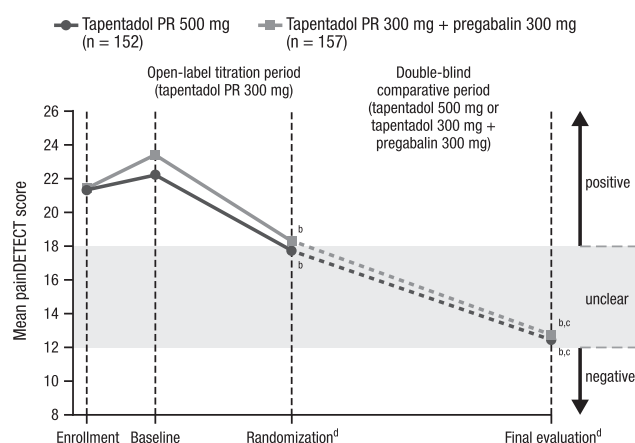


**Figure 4.** Results at randomization and final evaluation on the (A) PGIC and (B) CGIC (LOCF; full analysis set for the double-blind comparative arm). PGIC, patient global impression of change; CGIC, clinician global impression of change; LOCF, last observation carried forward.

### Neuropathic Pain Component

The mean (SD) painDETECT score (LOCF) at baseline was 22.2 (5.69) in the tapentadol PR group and 23.4 (5.94) in the tapentadol PR/pregabalin group of the full analysis set for the double-blind comparative arms. The mean painDETECT score (LOCF) decreased over time in both treatment groups (Figure 5). In the tapentadol PR and tapentadol PR/pregabalin groups, respectively, mean (SD) changes from baseline to final evaluation (LOCF) were  $-9.7$  (8.42) and  $-10.9$  (7.91; both  $P < 0.0001$  for the change from baseline) and mean (SD) changes from randomization to final evaluation (LOCF) were  $-5.8$  (8.66) and  $-6.1$  (7.42; both  $P < 0.0001$  for the change from randomization).

The mean NPSI total score (LOCF) at baseline was 62.2 (17.84) in the tapentadol PR group and 64.3 (19.00) in the tapentadol PR/pregabalin group. In the tapentadol PR and tapentadol PR/pregabalin groups, respectively, mean (SD) changes from baseline to final evaluation (LOCF) were  $-32.8$  (22.56) and  $-34.6$  (23.71) and mean (SD) changes from randomization to final evaluation (LOCF) were  $-16.4$  (18.83) and  $-16.7$  (19.85; all  $P < 0.0001$  for the change from baseline). Mean (SD) NPSI subscores at baseline are shown in Table S4. Mean NPSI subscores (LOCF) decreased over time, with significant improvements observed for all



**Figure 5.** PainDETECT scores over time (LOCF; full analysis set for the double-blind comparative arm).<sup>a</sup> LOCF, last observation carried forward; PR, prolonged release. <sup>a</sup>All patients received tapentadol PR 300 mg during the titration period (from baseline to randomization). <sup>b</sup> $P < 0.0001$  for the change from baseline. <sup>c</sup> $P < 0.0001$  for the change from randomization. <sup>d</sup>painDETECT scores at randomization were the last available scores before the first intake of study drug during the double-blind comparative period, and scores at final evaluation were the last available scores after the first intake of study drug during the double-blind comparative period.

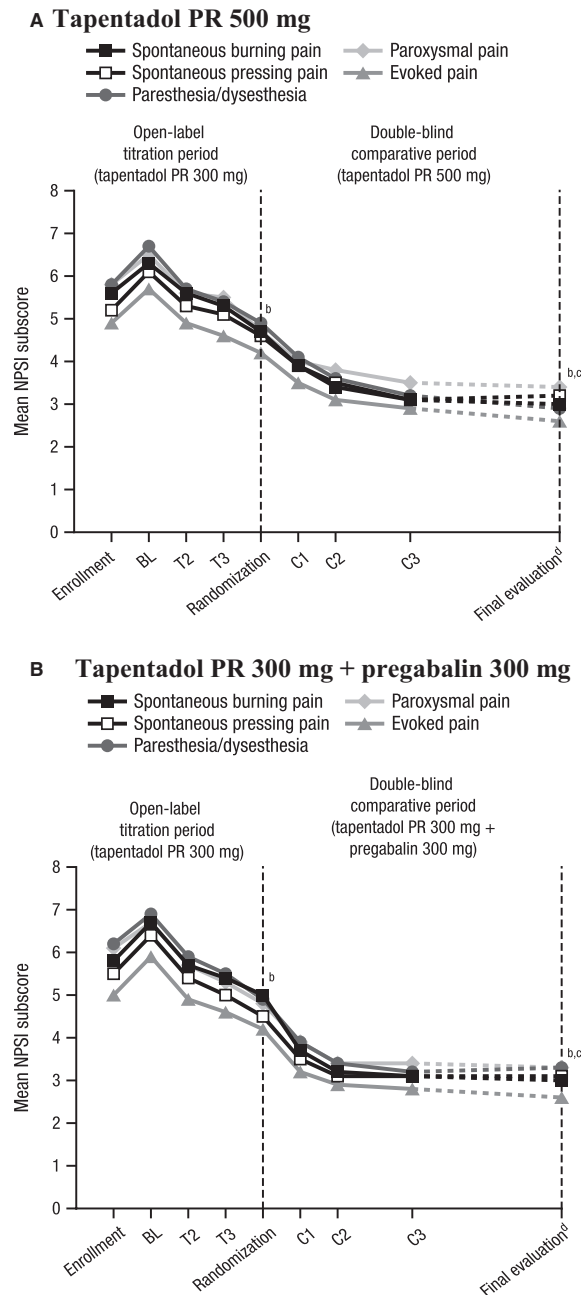
subscores in both treatment groups from baseline to final evaluation (all  $P < 0.0001$  for the change from baseline) and from randomization to final evaluation (all  $P < 0.0001$  for the change from randomization; Figure 6). In the tapentadol PR and tapentadol PR/pregabalin groups, respectively, of the full analysis set for the double-blind comparative arm, the percentages of patients with no pain attacks during the previous 24 hours, as reported on the NPSI (LOCF), were 4.6% (7/152) and 2.5% (4/157) at baseline, 7.9% (12/152) and 4.5% (7/157) at randomization, and 25.7% (39/152) and 18.5% (29/157) at final evaluation.

### Quality of Life and Function

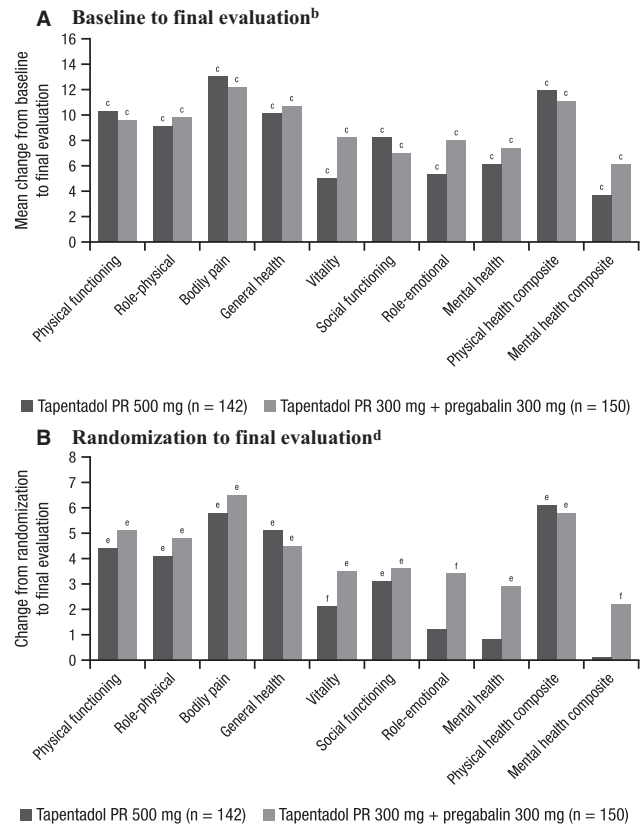
Mean (SD) SF-12 domain and composite scores at baseline are shown in Table S5. Significant and clinically meaningful ( $\geq 5$  points<sup>27</sup>) improvements from baseline to final evaluation were observed in all domain scores and the physical health composite score of the SF-12 (LOCF) in both treatment groups (all  $P < 0.0001$  for the change from baseline; Figure 7A). In the tapentadol PR/pregabalin group, all SF-12 subscale scores and both summary scores improved significantly from randomization to final evaluation (LOCF; all  $P < 0.05$  for the change from randomization; Figure 7B). In the tapentadol PR group, the SF-12 physical functioning, role-physical, bodily pain, general health, vitality and social functioning subscale scores and the physical health composite score improved significantly from randomization to final evaluation (LOCF; all  $P < 0.05$  for the change from randomization; Figure 7B).

In the tapentadol PR and tapentadol PR/pregabalin groups, respectively, mean (SD) EQ-5D health status index scores (LOCF) were 0.28 (0.312) and 0.18 (0.315) at baseline. The mean (SD) change from baseline to final evaluation (LOCF) in the EQ-5D health status index score was 0.34 (0.363) with tapentadol PR and 0.42 (0.390) with tapentadol PR/pregabalin (both  $P < 0.0001$  for the change from baseline). The mean (SD) change from randomization to final evaluation (LOCF) was 0.09 (0.323) for tapentadol PR and 0.09 (0.254) for tapentadol PR/pregabalin (both  $P < 0.05$  for the change from randomization). Similar improvements over the course of treatment were observed in the EQ-5D visual analog scale in both treatment groups.

At baseline, the mean (SD) HADS anxiety subscale score (LOCF) was 7.8 (4.61) in the tapentadol PR group and 8.8 (5.15) in the tapentadol PR/pregabalin group; in the tapentadol PR and tapentadol PR/pregabalin



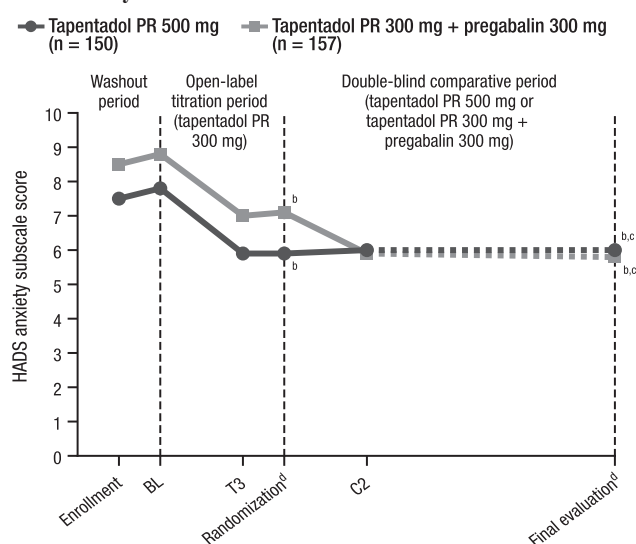
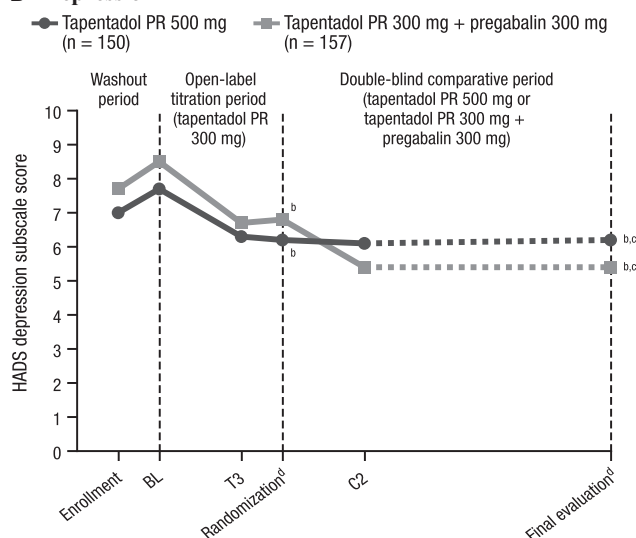
**Figure 6.** Mean NPSI subscores over time for patients randomized to (A) tapentadol PR 500 mg or (B) tapentadol PR 300 mg plus pregabalin 300 mg during the double-blind comparative period (LOCF; full analysis set for the double-blind comparative arm).<sup>a</sup> NPSI, Neuropathic Pain Symptom Inventory; PR, prolonged release; LOCF, last observation carried forward; BL, baseline; T, titration; C, comparative. <sup>a</sup>All patients received tapentadol PR 300 mg during the titration period (from baseline to randomization). <sup>b</sup> $P < 0.0001$  for the change from baseline for all subscores. <sup>c</sup> $P < 0.0001$  for the change from randomization for all subscores. <sup>d</sup>NPSI scores at randomization were the last available scores before the first intake of study drug during the double-blind comparative period, and scores at final evaluation were the last available scores after the first intake of study drug during the double-blind comparative period.



**Figure 7.** Mean changes in SF-12 subscale and composite scores from (A) baseline to final evaluation and (B) from randomization to final evaluation (LOCF; full analysis set for the double-blind comparative arm).<sup>a</sup> SF-12, Short Form-12; PR, prolonged release. <sup>a</sup>All patients received tapentadol PR 300 mg during the titration period (from baseline to randomization). <sup>b</sup>Results are for patients with baseline and final evaluation values. <sup>c</sup> $P < 0.0001$  for the change from baseline. <sup>d</sup>Results are for patients with randomization and final evaluation values. <sup>e</sup> $P < 0.0001$  for the change from randomization. <sup>f</sup> $P < 0.05$  for the change from randomization.

groups, significant improvements were observed from baseline to final evaluation (LOCF;  $-2.2$  [3.69] and  $-2.9$  [4.29], respectively; both  $P < 0.0001$  for the change from baseline) and from randomization to final evaluation ( $-0.3$  [2.97] and  $-1.2$  [3.35], respectively;  $P < 0.0001$  for the change from randomization for the tapentadol PR/pregabalin group; Figure 8A). The mean (SD) HADS depression subscale score at baseline (LOCF) was 7.7 (4.66) in the tapentadol PR group and 8.5 (4.80) in the tapentadol PR/pregabalin group. Significant improvements were also observed in the mean HADS depression subscale score for patients taking tapentadol PR and tapentadol PR/pregabalin from baseline to final evaluation (LOCF;  $-1.8$  [3.56] and  $-3.0$  [3.98], respectively; both  $P < 0.0001$  for the change from baseline) and from randomization to final



**A Anxiety****B Depression**

**Figure 8.** Mean HADS (A) anxiety and (B) depression subscale scores over time (LOCF; full analysis set for the double-blind comparative arm). <sup>a</sup>HADS, Hospital Anxiety and Depression Scale; LOCF, last observation carried forward; PR, prolonged release; BL, baseline; T, titration period; C, comparative period; SD, standard deviation. <sup>a</sup>All patients received tapentadol PR 300 mg during the titration period (from baseline to randomization). <sup>b</sup> $P < 0.0001$  for the change from baseline. <sup>c</sup> $P < 0.0001$  for the change from randomization. <sup>d</sup>HADS scores at randomization were the last available scores before the first intake of study drug during the double-blind comparative period, and scores at final evaluation were the last available scores after the first intake of study drug during the double-blind comparative period.

evaluation ( $-0.4$  [3.06] and  $-1.3$  [2.96], respectively;  $P < 0.0001$  for the change from randomization for the tapentadol PR/pregabalin group; Figure 8B).

In the tapentadol PR and tapentadol PR/pregabalin groups, the mean time that patients slept (LOCF)

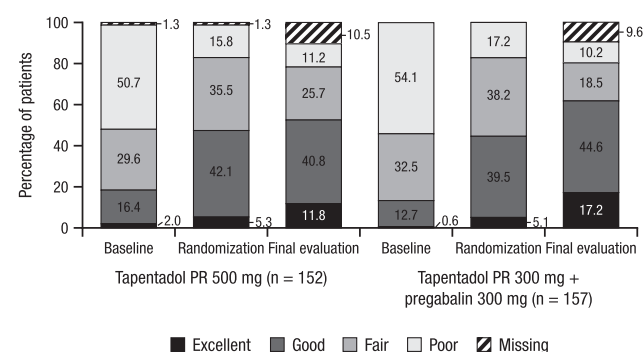
increased significantly from baseline to final evaluation (both  $P < 0.0001$  for the change from baseline) and from randomization to final evaluation (both  $P < 0.05$  for the change from randomization). In the tapentadol PR and tapentadol PR/pregabalin groups, the mean number of awakenings that patients experienced per night (LOCF) decreased over time in both treatment groups; the mean number of awakenings decreased significantly from baseline to final evaluation in both treatment groups (both  $P < 0.0001$  for the change from baseline). The mean time to fall asleep (LOCF) did not change significantly in either treatment group from baseline to final evaluation or from randomization to final evaluation. The overall quality of sleep (LOCF) improved similarly in both treatment groups over time (Figure 9).

Pain intensity, subject satisfaction with treatment, PGIC, CGIC, NPSI, EQ-5D, SF-12, and HADS results were generally comparable for analyses in the full analysis set for the double-blind comparative arm using LOCF and using observed-case analysis (Tables S1–S7).

**Tolerability**

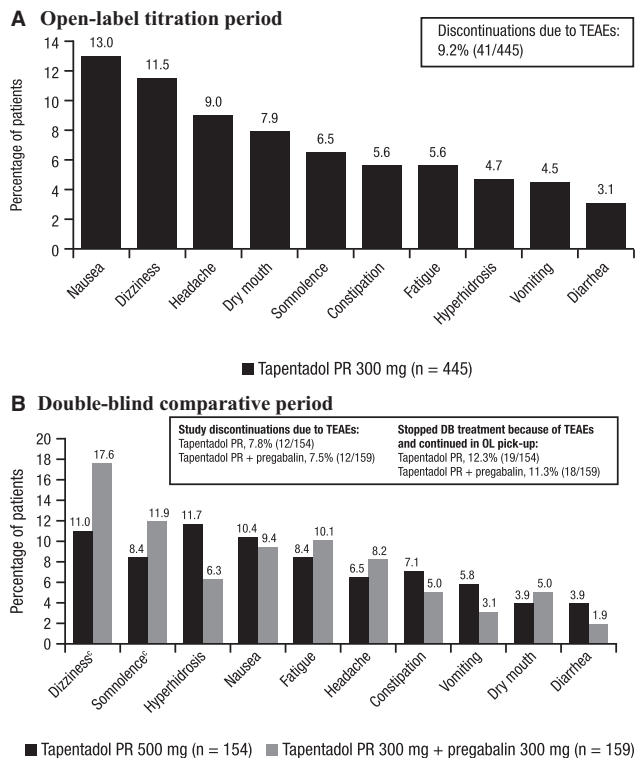
During the open-label titration period, a total of 51.0% (227/445) of patients in the safety population for the open-label phase reported  $\geq 1$  TEAE. The most common TEAEs (incidence  $\geq 5\%$ ) are summarized in Figure 10A.

In the tapentadol PR and tapentadol PR/pregabalin groups, respectively, 63.6% (98/154) and 64.8% (103/159) of patients reported  $\geq 1$  TEAE. The most common TEAEs (incidence  $\geq 5\%$  in either treatment group) and other selected TEAEs during the double-blind comparative period are summarized in Figure 10B. The safety



**Figure 9.** Overall sleep quality ratings on the Sleep Evaluation Questionnaire at baseline, randomization, and final evaluation (LOCF; full analysis set for the double-blind comparative arm). LOCF, last observation carried forward; PR, prolonged release.





**Figure 10.** TEAEs reported by  $\geq 5\%$  of patients in (A) the overall safety population during the open-label titration period and (B) either treatment group during the double-blind comparative period (safety set for the double-blind comparative arm).<sup>a,b</sup> TEAE, treatment-emergent adverse event; PR, prolonged release; DB, double-blind; OL, open-label. <sup>a</sup>Incidence is based on the number of patients experiencing  $\geq 1$  TEAE, not the number of TEAEs. <sup>b</sup>Selected TEAEs with an incidence  $< 5\%$  in either treatment group were also included. <sup>c</sup>Based on a post hoc analysis, the incidence of the composite of dizziness and/or somnolence was significantly lower in the tapentadol PR group (16.9% [26/154]) than in the tapentadol PR/pregabalin group (27.0% [43/159];  $P = 0.0302$ ).

and tolerability profile for tapentadol PR during the titration period and in the monotherapy arm was in line with previous trials<sup>15,17,28,29</sup> and remained favorable in the high dose range of 500 mg/day. In the tapentadol PR/pregabalin group, the increase in TEAEs was much smaller than in historical trials of combinations of opioids and anticonvulsants.<sup>10,11</sup> Based on a post hoc analysis, the incidence of the composite of the 2 most common TEAEs (dizziness and/or somnolence) was significantly lower in the tapentadol PR group (16.9% [26/154]) than in the tapentadol PR/pregabalin group (27.0% [43/159];  $P = 0.0302$ ).

During the double-blind comparative period, the worst intensity of related TEAEs was severe for 2.2% (4/186) of TEAEs reported in the tapentadol PR group and for 8.4% (17/203) of TEAEs reported in the

tapentadol PR/pregabalin group. Serious TEAEs were reported by 3.2% (5/154) of patients in the tapentadol PR group during the comparative period; the serious TEAEs reported (chest injury, fall, tachycardia, vertigo, upper abdominal pain, and flank pain) were all single occurrences. A total of 1.9% (3/159) of patients in the tapentadol PR/pregabalin group reported serious TEAEs; these serious TEAEs were reported as occurring only once during the comparative period and included nausea, goiter, chest pain, hyperhidrosis, and thrombosis.

During the open-label titration period, 9.2% (41/445) of patients in the safety population for the open-label phase discontinued treatment because of TEAEs (Figure 10A). During the double-blind comparative period, 7.8% (12/154) of patients in the tapentadol PR group and 7.5% (12/159) of patients in the tapentadol PR/pregabalin group discontinued the study because of TEAEs (Figure 10B). In addition, 12.3% (19/154) of patients in the tapentadol PR group and 11.3% (18/159) of patients in the tapentadol PR/pregabalin group stopped treatment in the double-blind comparative period because of TEAEs and continued treatment in the open-label pickup arm.

## DISCUSSION

Patients with severe, chronic low back pain are often treated with combination therapy.<sup>30</sup> Results of the international CHANGE PAIN physician survey, conducted over a 15-month period in 2009 and 2010, showed that 93.2% of responding physicians reported treating patients with severe, chronic low back pain with combination therapy.<sup>30</sup> A combination of an opioid and a co-analgesic (eg, anticonvulsant, antidepressant) is one of the most commonly used types of combination therapy for severe, chronic low back pain.<sup>30</sup> Despite the relative frequency of combination therapy use, combination therapy with an opioid and a co-analgesic may not be the best option for addressing pain with a neuropathic component. Results of a meta-analysis of the data from 2 studies in patients with painful diabetic peripheral neuropathy showed that combination therapy with gabapentin and an opioid (morphine or oxycodone CR) resulted in only modest gains in efficacy and was associated with a higher rate of AE-related discontinuations than monotherapy with gabapentin.<sup>11</sup> Therefore, it is of interest to evaluate the potential of monotherapy and combination therapy with newer analgesic options, such as tapentadol PR, for treating low back pain with a neuropathic component.

The current study was conducted to determine whether monotherapy with tapentadol PR, which has both MOR agonist and NRI activities and, thus, may address both nociceptive and neuropathic mechanisms of chronic pain, would provide comparable pain relief to combination therapy with tapentadol PR and a co-analgesic (pregabalin) in patients with low back pain with a neuropathic pain component. The first challenge of conducting this study was the selection of an appropriate target population with mixed pain that might be managed with combination therapy in usual clinical practice. The selection of this target population was based on the results of the painDETECT questionnaire<sup>21</sup> (which showed that the selected patients had a neuropathic component to their low back pain) and supported by the baseline characteristics observed for these patients who had neuropathic pain symptoms (based on the results of the NPSI<sup>22</sup>), a long history of low back pain, and a high incidence of lumbar radiculopathy, as well as a high baseline pain intensity score. The mean baseline pain intensity score in the current study was 8.4 in both treatment groups, which was higher than that in previous studies of tapentadol PR in patients with moderate-to-severe, diabetic peripheral neuropathic pain (7.4),<sup>16</sup> or severe, low back pain with or without a neuropathic pain component (7.4).<sup>19</sup>

The second challenge of conducting this study was selecting a comparator for tapentadol PR monotherapy. Although evidence showing the efficacy of pregabalin in low back pain with a neuropathic component and radiculopathy is not unequivocally positive, pregabalin was selected as the co-analgesic for the combination therapy arm in part because it is considered a first-line treatment for several different types of neuropathic pain.<sup>31</sup> In addition, pregabalin was chosen as a comparator in the combination therapy arm because unlike many of the antidepressants that are often used for combination therapy with an opioid,<sup>31</sup> its mechanism of action is distinctly different from and complementary to that of tapentadol. A placebo comparator was not used in this study because efficacy in neuropathic pain has been previously demonstrated in placebo-controlled trials for both tapentadol PR<sup>16</sup> and pregabalin.<sup>32,33</sup> Furthermore, the use of a placebo control in this population of patients with severe pain would have been difficult to justify ethically.

In a previous study evaluating the combination of a strong opioid (oxycodone PR) with a co-analgesic (gabapentin) for the management of pain related to diabetic peripheral neuropathy,<sup>10</sup> combination therapy

was associated with improved efficacy compared with monotherapy, but was associated with a higher incidence of central nervous system-related AEs and AE-related discontinuations. In the current study, the analgesic effectiveness provided by tapentadol PR (500 mg/day) was noninferior to that provided by a combination of tapentadol PR (300 mg/day) and pregabalin (300 mg/day) in a population of patients preselected for a response to tapentadol PR 300 mg. Both treatment arms had similar significant and clinically relevant improvements in measures of neuropathic pain in patients with severe low back pain with a neuropathic component. Secondary efficacy evaluations showed that tapentadol PR monotherapy and tapentadol PR/pregabalin combination therapy were associated with comparable improvements in quality-of-life measures (SF-12 and EQ-5D). Significant improvements from randomization to final evaluation were observed in all 8 subscale scores and both composite scores for the tapentadol PR/pregabalin group, and in the physical functioning, role-physical, bodily pain, general health, vitality, social functioning subscale scores, and the physical health composite score for tapentadol PR monotherapy.

Although larger improvements were observed in the tapentadol PR/pregabalin group, significant improvements were also observed in HADS anxiety and depression subscale scores from randomization to final evaluation in both treatment groups. Unlike previous trials of opioids with co-analgesics,<sup>10,11</sup> the combination of tapentadol PR with pregabalin used in the current study did not result in higher incidences of discontinuations. However, the incidence of the composite of dizziness and/or somnolence was significantly higher for patients taking combination therapy with tapentadol PR plus pregabalin than for those taking tapentadol PR monotherapy.

Historical data suggest a modest gain in efficacy and an increase in side effects and related treatment discontinuation with combination therapy with a strong opioid and a centrally acting co-analgesic,<sup>7,10,11</sup> which is frequently used in practice for severe chronic low back pain and neuropathic pain.<sup>7,9</sup> Results of the current study indicate that tapentadol PR monotherapy, which has both MOR agonist and NRI activities,<sup>12</sup> is a viable treatment option for managing severe chronic low back pain with a neuropathic component and offers advantages in terms of central nervous system tolerability over combination therapy with pregabalin. Based on the favorable side effect profile observed in the current trial and in previous trials compared with classical opioid analgesics,<sup>15,17,28,29</sup>

tapentadol PR may also be a preferred combination partner to pregabalin or other centrally acting co-analgesics with a similar mechanism of action for patients benefiting from combination therapy. Further studies might identify subgroups of patients who would benefit most from monotherapy or combination therapy.

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## SUPPORTING INFORMATION

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

**Table S1.** Mean (SD) Pain Intensity Scores (11-point NRS-3) at Baseline, Randomization, and Final Evaluation

Using LOCF and Observed-case Analysis (Full Analysis Set for the Double-blind Comparative Arm)

**Table S2.** Subject Satisfaction With Treatment Ratings at Baseline, Randomization, and Final Evaluation Using LOCF and Observed-case Analysis (Full Analysis Set for the Double-blind Comparative Arm)

**Table S3.** (A) PGIC and (B) CGIC Ratings at Baseline, Randomization, and Final Evaluation Using LOCF and Observed-case Analysis (Full Analysis Set for the Double-blind Comparative Arm)

**Table S4.** NPSI Results in the Baseline painDETECT Unclear/Positive Subset: (A) Mean (SD) NPSI Overall Feeling and Subscores and (B) Total Number of Pain Attacks Within the Past 24 Hours at Baseline, Randomization, and Final Evaluation Using LOCF and Observed-case Analysis (Full Analysis Set for the Double-blind Comparative Arm)

**Table S5.** Mean (SD) SF-12 Scores at Baseline, Randomization, and Final Evaluation Using Observed-case Analysis in the Full Analysis Set for the Double-blind Comparative Arm and Using the LOCF in the Per Protocol Set

**Table S6.** Mean (SD) EQ-5D Health Status Index Score at Baseline, Randomization, and Final Evaluation Using LOCF and Observed-case Analysis (Full Analysis Set for the Double-blind Comparative Arm)

**Table S7.** Mean (SD) HADS Anxiety and Depression Subscale Scores at Baseline, Randomization, and Final Evaluation Using LOCF and Observed-case Analysis (Full Analysis Set for the Double-blind Comparative Arm)