# Effects of Tapentadol Prolonged Release (PR) Versus Oxycodone/Naloxone PR on Quality of Life and Function Measures in Patients With Severe Chronic Low Back Pain With a Neuropathic Pain Component

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## ABSTRACT

**Purpose:** **Severe chronic pain, particularly that associated with a neuropathic pain component, can have a significant negative impact on health-related quality of life. Tapentadol prolonged release (PR), a centrally acting analgesic with μ-opioid receptor agonist and noradrenaline reuptake inhibitor activities, has been shown to be effective and well tolerated for managing severe chronic low back pain with or without a neuropathic component, and has been associated with significant improvements in health-related quality of life in these patients. A fixed-dose combination of oxycodone/naloxone PR has also been shown to be effective for managing moderate to severe chronic low back pain and improving quality of life. An equianalgesic ratio of approximately 5:1 has been established for tapentadol PR versus oxycodone PR in earlier randomized, controlled trials. This study evaluated the impact of tapentadol PR and oxycodone/naloxone PR on quality of life and function measures as secondary outcomes in patients with severe chronic low back pain with a neuropathic pain component. Results for the quality of life and function measures are presented here; results for the 2 co-primary endpoints, secondary effectiveness endpoints, and safety and tolerability outcomes are presented in separate abstracts.**

**Methods:** **In this randomized, controlled, open-label, phase IIIb/IV study, eligible patients with severe pain (average pain intensity ≥6 on an 11-point numerical rating scale-3 [NRS-3; average 3-day pain intensity] at baseline and a rating of "positive" or "unclear" on the painDETECT questionnaire at baseline) were randomized to twice-daily tapentadol PR 50 mg or oxycodone/naloxone PR 10 mg/5 mg. After a 21-day titration period (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. Quality of life and function were evaluated using the Short Form-12 (SF-12) and EuroQol-5 Dimension (EQ-5D) questionnaires. Patients and investigators reported their impression of the overall change in a patients' condition since starting treatment on the patient global impression of change (PGIC) and clinician global impression of change (CGIC), respectively. An analysis of covariance (ANCOVA) model, including treatment and pooled centers as factors and baseline value as a covariate, was used to evaluate the SF-12 and EQ-5D in the full analysis set. The last observation carried forward (LOCF) was used for imputing missing assessments.**

**Results:** **With tapentadol PR (*n* = 130), significant improvements from baseline to final evaluation were observed in both SF-12 summary scores (least-squares [LS] mean [standard error of the mean (SEM)] change from baseline to final evaluation: physical component summary, 9.74 [0.795]; mental component summary, 3.08 [0.846]) and all domain scores (physical functioning, 8.36 [0.826]; role-physical, 7.26 [0.712]; bodily pain, 10.99 [0.946]; general health, 8.45 [0.870]; vitality, 4.94 [0.806]; social functioning, 5.25 [0.887]; role-emotional, 4.76 [0.947]; and mental health, 5.16 [0.839]; all *P* <0.001). With oxycodone/naloxone PR (n = 125), significant improvements were observed in the SF-12 physical component summary score (LS mean [SEM] change from baseline to final evaluation, 6.20 [0.806]) and physical functioning (5.07 [0.836]), role-physical (4.67 [0.722]), bodily pain (7.46 [0.957]), general health (4.31 [0.882]), social functioning (2.29 [0.900]), role-emotional (2.59 [0.981]), and mental health (2.97 [0.858]) domain scores (all *P* <0.012). Improvements in the SF-12 physical component summary score and physical functioning, role-physical, bodily pain, general health, vitality, and social functioning domain scores were significantly greater with tapentadol PR than with oxycodone/naloxone PR (*P* ≤0.017). With tapentadol PR and oxycodone/naloxone PR, respectively, mean (standard deviation) EQ-5D health status index scores were 0.32 (0.295) and 0.34 (0.311) at baseline and 0.67 (0.317) and 0.57 (0.314) at final evaluation. EQ-5D scores improved significantly from baseline to final evaluation in both treatment groups (LS mean [SEM] change from baseline to final evaluation: tapentadol PR, 0.34 [0.028]; oxycodone/naloxone PR, 0.24 [0.028]; both *P* <0.001), with significantly greater improvement with tapentadol PR versus oxycodone/naloxone PR (*P* = 0.010). With tapentadol PR and oxycodone/naloxone PR, respectively, ratings of "very much improved" or "much improved" were reported by 54.3% (70/129) and 29.6% (37/125) of patients on the PGIC and by 59.4% (76/128) and 35.0% (43/123) of investigators on the CGIC at final evaluation.**

**Conclusions:** **Tapentadol PR was associated with greater improvements in quality of life and function measures than oxycodone/naloxone PR in opioid-naive patients with severe chronic low back pain with a neuropathic pain component. The favorable effects of tapentadol PR versus oxycodone/naloxone PR on quality of life were consistently shown across different validated measures and coincided with improvements in effectiveness and tolerability outcomes (as described separately). In conclusion, tapentadol PR can be proposed as a preferred option for treating severe chronic pain with a neuropathic pain component.**

## INTRODUCTION

- Neuropathic pain may have detrimental effects on health-related quality of life[1]
- Chronic low back pain is often accompanied by a neuropathic pain component, which often complicates pain management[2,3]
- Tapentadol is a centrally acting analgesic with μ-opioid receptor agonist and noradrenaline reuptake inhibitor activities[4,5]
  - Tapentadol prolonged release (PR) has been shown to be efficacious and well tolerated for managing severe chronic low back pain with or without a neuropathic component in recent phase IIIb studies[4,5]
    - In those phase IIIb studies,[4,5] tapentadol PR was also associated with significant improvements in health-related quality of life in patients with severe chronic low back pain with or without a neuropathic pain component
  - In addition, tapentadol has been shown to be effective and well tolerated for the management of moderate to severe chronic osteoarthritis knee pain,[6,7] low back pain,[7,8] pain related to diabetic peripheral neuropathy[7] and cancer pain[9–12] with improved tolerability (particularly gastrointestinal tolerability) compared with oxycodone controlled release (CR; for osteoarthritis pain, low back pain, and cancer pain)[6–8,11] and morphine CR (for cancer pain)[9,10,12]
- A fixed-dose combination of oxycodone/naloxone PR has been shown to be effective and well tolerated for the management of moderate to severe chronic low back pain,[13] with better gastrointestinal tolerability compared with oxycodone PR alone[13,14]
  - The naloxone component of oxycodone/naloxone PR is an opioid antagonist that acts on the opioid receptors in the gut, reducing opioid-induced constipation by blocking the effects of oxycodone on these receptors[14]

## OBJECTIVES

- To evaluate the effects of tapentadol PR versus oxycodone/naloxone PR on quality of life and function measures in non-opioid pre-treated patients with uncontrolled, severe chronic low back pain with a neuropathic pain component
- Effectiveness, tolerability, and safety results from this study are presented separately at this congress in the following posters:
  - Effectiveness results: Baron R, et al. *Effectiveness of tapentadol prolonged release (PR) versus oxycodone/naloxone PR for severe chronic low back pain with a neuropathic pain component*
  - Tolerability and safety results: Binder A, et al. *Safety and tolerability of tapentadol prolonged release (PR) versus oxycodone/naloxone PR for severe chronic low back pain with a neuropathic pain component*

## METHODS

### Patients

- Key trial-specific inclusion criteria
  - Diagnosis of chronic low back pain lasting ≥3 months prior to enrollment
  - Pain requiring a strong (World Health Organization [WHO] step III) analgesic, based on the investigator's assessment at enrollment
  - Score on the painDETECT questionnaire[15] (used to evaluate the likelihood of a neuropathic pain component to low back pain; possible score of 0–38) of "positive" (score of 19–38) or "unclear" (score of 13–18) at enrollment
    - For patients taking a stable regimen of centrally acting co-analgesics, which must have been washed out prior to randomization, a "negative" painDETECT score was permitted at enrollment if that score was ≥9
    - All patients were required to have an "unclear" or "positive" painDETECT score at randomization
  - For patients not taking co-analgesics at enrollment, average pain intensity score ≥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") at enrollment
    - For patients taking co-analgesics at enrollment, which must have been washed out prior to randomization, average pain intensity score ≥5 on an 11-point NRS-3
    - All patients were required to have an average pain intensity score ≥6 on an 11-point NRS at randomization
- Key trial-specific exclusion criteria
  - Low back pain caused by cancer and/or metastatic diseases
  - Severe renal impairment or history of or current laboratory values reflecting moderate or severe hepatic impairment
  - History of seizure disorder or epilepsy; mild or moderate traumatic brain injury, stroke, transient ischemic attack, or brain neoplasm within 1 year; or severe traumatic brain injury within 15 years or residual sequelae suggesting transient changes in consciousness
  - Known or suspected paralytic ileus, acute biliary obstruction, or acute pancreatitis
- Permitted medications
  - For patients on a stable pre-study regimen of non-steroidal anti-inflammatory drugs (NSAIDs) or paracetamol, these medications were permitted at the same stable dose
  - Selective serotonin reuptake inhibitors (for the treatment of uncomplicated depression) were permitted if patients had been taking a stable dose for ≥30 days prior to the randomization visit
  - Other medications used to treat psychiatric or neurological disorders were permitted if patients had been taking a stable dose for ≥3 months prior to the randomization visit
- Prohibited medications
  - All analgesics and co-analgesics, except for study drug and stable doses of NSAIDs and paracetamol, 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 the randomization visit and during the study
  - Laxatives and antiemetics as prophylaxis were prohibited within 14 days prior to the randomization visit and during the study
  - Monoamine oxidase inhibitors were prohibited within 14 days prior to the randomization visit and during the study

### Study Design

- This randomized, multicenter, parallel-arm, open-label, active-controlled, phase IIIb/IV study (ClinicalTrials.gov Identifier: NCT01338616) included an optional 3- to 14-day washout period, a 3-week titration period, and a 9-week continuation period (**Figure 1**)

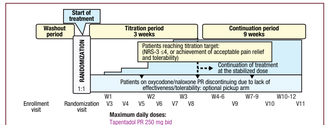



**Figure 1. Study design.**

- During the washout period (mandatory in patients taking a centrally acting analgesic or co-analgesic at enrollment; to be completed prior to starting study treatment), centrally acting analgesics and co-analgesics were discontinued prior to the randomization visit; 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 or oxycodone/naloxone PR 10 mg/5 mg bid at minimal 3-day intervals until the minimum target of titration was reached (maximum permitted dose, tapentadol PR 250 mg bid or 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 1 of the following:
    - NRS-3 ≤4 with acceptable tolerability as reported by the patient
    - NRS-3 ≤5 if pain relief and tolerability were reported by the patient and investigator as satisfactory to continue in the study, and 1) the patient was on the maximum dose of tapentadol PR or oxycodone/naloxone PR or 2) 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 due to intolerable side effects or a lack of efficacy could be switched to tapentadol PR in a group arm or discontinued from the study (if they did not want to switch to tapentadol PR). The option to switch to the pickup arm due to 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

- Quality of life was evaluated as a secondary outcome in this study using the Short Form-12 (SF-12) Health Survey and the EuroQol-5 Dimension (EQ-5D) health status questionnaire
  - The SF-12 Health Survey[16] includes 12 questions that are 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 ("lowest level of health") to 100 ("highest level of health")
  - The EQ-5D[17] health status questionnaire includes 5 dimensions of health-related quality of life (mobility, self-care, usual activities, pain or discomfort, and anxiety or depression); patients rated each dimension using a 3-point scale (1 = "no problems," 2 = "some problems," 3 = "extreme problems")
    - In addition to the 5 dimensions, a score for the patient's health state was recorded on a 0 ("worst imaginable health state") to 100 ("best imaginable health state") visual analog scale (VAS)
  - The EQ-5D health status questionnaire and SF-12 Health Survey were 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 patient global impression of change (PGIC) and clinician global impression of change (CGIC) were used to evaluate patients' global health status
  - For the PGIC, 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, investigators rated patients' global improvement and satisfaction with the treatment using the same 7-point scale as the PGIC
  - 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
- The mean daily doses of tapentadol PR and oxycodone/naloxone PR were evaluated during the titration and continuation periods
- Lumbar radiculopathy was diagnosed according to the following criteria:
  - Dermatomal pain present, radiating beyond the knee toward the foot, and evoked by stretching of the sciatic nerve, and ≥1 of the following signs of root dysfunction:
    - Sensory impairment with motor symptoms
    - And/or absent or diminished reflexes related to affected dermatome(s)
    - And/or signs of root dysfunction in quantitative sensory testing

### Statistical Analyses

- This study had an adaptive 3-stage, group-sequential design (O'Brien and Fleming type design[18]); the results presented here are those of the final analysis
- A 2-sample *t* test was used for the calculation of the sample size
  - This study had 2 primary endpoints: the change in average pain intensity (11-points NRS-3) from baseline to final evaluation and the change in the Patient Assessment of Constipation Symptoms total score from baseline to final evaluation
  - For both primary endpoints, a sample size of 96 patients per group in the per-protocol set was required to show the non-inferiority of tapentadol PR as compared to 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 primary endpoints are explained in further detail in the effectiveness and tolerability and safety posters
- The safety set included all randomized patients who took ≥1 dose of study drug
- The full analysis set included all randomized patients who took ≥1 dose of study drug and had ≥1 post-baseline pain intensity assessment (NRS-3)
- The per-protocol set 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 SF-12 Health Survey, physical and mental component summary scores (possible score for each, 0 ["lowest level of health"] to 100 ["highest level of health"]) were calculated by combining scores from the 12 individual questions
- The responses to each of the EQ-5D dimensions 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 changes from baseline to final evaluation in the SF-12 domain scores and composite scores and the EQ-5D health status index score and VAS score were evaluated in the full analysis set using an analysis of covariance (ANCOVA) model including treatment and pooled centers as factors and score at baseline as a covariate
- Between-group differences in PGIC and CGIC scores were evaluated using Fisher's exact test
- The last observation carried forward (LOCF) was used for imputing missing scores
- All analyses presented in this poster were for secondary endpoints, and the respective analyses were exploratory and not adjusted for multiplicity

## RESULTS

### Patients

- The safety set included 258 patients (tapentadol PR, *n* = 130; oxycodone/naloxone PR, n = 128), and the full analysis set included 256 patients (tapentadol PR, n = 130; oxycodone/naloxone PR, n = 126)
- Demographic characteristics were similar in both treatment groups in the safety set
  - All patients in both treatment groups were white, and >50% were female (tapentadol PR, 59.2% [77/130]; oxycodone/naloxone PR, 65.6% [84/128])
  - The mean (standard deviation [SD]) age was 58.1 (11.48) years in the tapentadol PR group and 58.4 (12.23) years in the oxycodone/naloxone PR group
- A total of 58.5% (76/130) of patients in the tapentadol PR group and 57.9% (73/126) of patients in the oxycodone/naloxone PR group had a diagnosis of lumbar radiculopathy in the full analysis set at baseline (**Figure 2**)
- 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
- 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), respectively

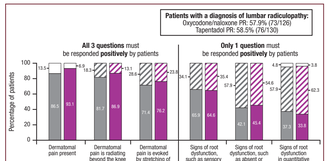
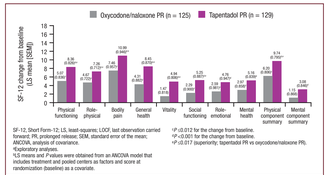



**Figure 2. Diagnosis of lumbar radiculopathy (full analysis set).**

### Quality of Life and Function

- In the tapentadol PR group of the full analysis set, significant improvements were observed in all SF-12 domain scores from baseline to final evaluation (LOCF), as well as in both SF-12 summary scores (all *P* <0.001; **Figure 3**)
  - In the oxycodone/naloxone PR group, significant improvements from baseline to final evaluation were observed in the SF-12 physical component summary score and in the SF-12 physical functioning, role-physical, bodily pain, general health, social functioning, role-emotional, and mental health domain scores (all *P* ≤0.012; **Figure 3**)
  - The improvements observed in the tapentadol PR group from baseline to final evaluation were significantly greater than in the oxycodone/naloxone PR group for the physical component summary score and for the physical functioning, role-physical, bodily pain, general health, vitality, and social functioning domain scores (all *P* ≤0.017; **Figure 3**)
    - At final evaluation, tapentadol PR was associated with greater improvements in the SF-12 domain and summary scores compared with oxycodone/naloxone PR, as follows (percent difference between tapentadol PR and oxycodone/naloxone PR): physical functioning, 64.8%; role-physical, 55.5%; bodily pain, 47.4%; general health, 96.0%; vitality, 236.7%; social functioning, 129.5%; role-emotional, 84.2%; mental health, 73.5%; physical component summary, 57.0%; and mental component summary, 168.5%




SF-12, Short Form-12; LS, least-squares; LOCF, last observation carried forward; PR, prolonged release; SEM, standard error of the mean; ANCOVA, analysis of covariance.
aExploratory analyses.
bLS means and *P* values were obtained from an ANCOVA model that includes treatment and pooled centers as factors and score at randomization (baseline) as a covariate.

**Figure 3. Change from baseline to final evaluation in SF-12 domain and summary scores (LS mean; LOCF; full analysis set).a,b**

- EQ-5D health status index scores at baseline and final evaluation are shown in **Figure 4A**
  - Significant increases were observed from baseline to final evaluation (LOCF) in the EQ-5D health status index score in both treatment groups in the full analysis set (both *P* <0.001; **Figure 4B**)
  - The improvement from baseline to final evaluation in the EQ-5D health status index score was significantly greater in the tapentadol PR group than in the oxycodone/naloxone PR group (*P* = 0.010; **Figure 4B**)
- EQ-5D health state assessment scores at baseline and final evaluation are shown in **Figure 4C**
  - Significant increases were also observed from baseline to final evaluation (LOCF) in the EQ-5D health state assessment in both the tapentadol PR group and the oxycodone/naloxone PR group (both *P* <0.001; **Figure 4D**)
  - The improvement from baseline to final evaluation in the EQ-5D health state assessment was significantly greater in the tapentadol PR group than in the oxycodone/naloxone PR group (*P* = 0.024; **Figure 4D**)

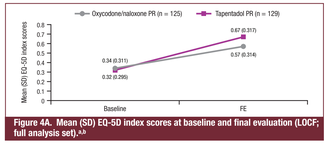
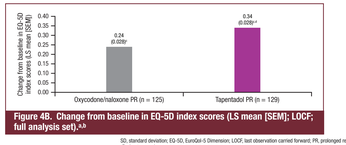



**Figure 4A. Mean (SD) EQ-5D index scores at baseline and final evaluation (LOCF; full analysis set).a,b**




SD, standard deviation; EQ-5D, EuroQol-5 Dimension; LOCF, last observation carried forward; PR, prolonged release; FE, final evaluation; LS, least-squares; SEM, standard error of the mean; ANCOVA, analysis of covariance.
aExploratory analyses.
bLS means and *P* values are obtained from an ANCOVA model that includes treatment and pooled centers as factors and score at randomization (baseline) as a covariate.
c*P* <0.001 for the change from baseline.
d*P* = 0.010 (superiority; tapentadol PR vs oxycodone/naloxone PR).
e*P* = 0.024 (superiority; tapentadol PR vs oxycodone/naloxone PR).

**Figure 4B. Change from baseline in EQ-5D index scores (LS mean [SEM]; LOCF; full analysis set).a,b**

- 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* = 0.0031; LOCF; **Figures 5A** and **5B**)
  - Overall, based on PGIC results, most patients 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)

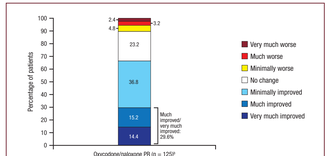



**Figure 5A. PGIC ratings at final evaluation for oxycodone/naloxone PR (LOCF; full analysis set).a**

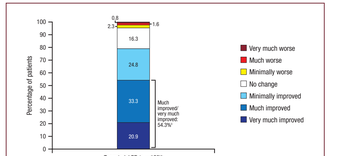



**Figure 5B. PGIC ratings at final evaluation for tapentadol PR (LOCF; full analysis set).a**

PGIC, patient global impression of change; PR, prolonged release; LOCF, last observation carried forward.
aExploratory analyses.
bValues are the numbers of patients with PGIC results available for final evaluation.
c*P* = 0.0031 vs oxycodone/naloxone PR.

- 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* = 0.0022; LOCF; **Figures 6A** and **6B**)
  - Overall, based on CGIC results, investigators rated patients' overall condition more favorably at final evaluation with tapentadol PR than with oxycodone/naloxone PR (*P* = 0.005)

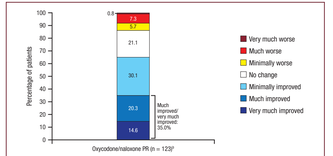



**Figure 6A. CGIC ratings at final evaluation for oxycodone/naloxone PR (LOCF; full analysis set).a**

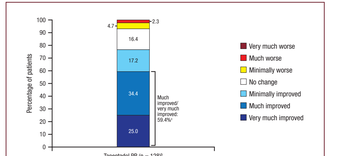



**Figure 6B. CGIC ratings at final evaluation for tapentadol PR (LOCF; full analysis set).a**

CGIC, clinician global impression of change; PR, prolonged release; LOCF, last observation carried forward.
aExploratory analyses.
bValues are the numbers of patients with CGIC results available for final evaluation.
c*P* = 0.0022 vs oxycodone/naloxone PR.

- EQ-5D health state assessment scores at baseline and final evaluation are shown in **Figure 4C**
  - Significant increases were also observed from baseline to final evaluation (LOCF) in the EQ-5D health state assessment in both the tapentadol PR group and the oxycodone/naloxone PR group (both *P* <0.001; **Figure 4D**)
  - The improvement from baseline to final evaluation in the EQ-5D health state assessment was significantly greater in the tapentadol PR group than in the oxycodone/naloxone PR group (*P* = 0.024; **Figure 4D**)

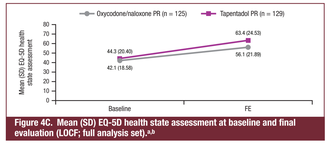



**Figure 4C. Mean (SD) EQ-5D health state assessment at baseline and final evaluation (LOCF; full analysis set).a,b**

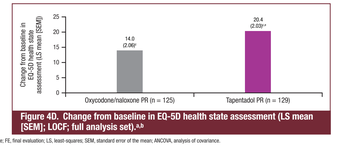



**Figure 4D. Change from baseline in EQ-5D health state assessment (LS mean [SEM]; LOCF; full analysis set).a,b**

## CONCLUSIONS

- **Tapentadol PR was associated with greater improvements in quality of life and function measures versus oxycodone/naloxone PR in non-opioid pre-treated patients with severe chronic low back pain with a neuropathic pain component**
- **The favorable effects of tapentadol PR versus oxycodone/naloxone PR on quality of life were consistently shown across different validated measures (including SF-12, EQ-5D, PGIC, and CGIC) and coincided with improvements in effectiveness and tolerability outcomes (as described separately)**
  - **Tapentadol PR was associated with significantly improved quality of life and function compared with oxycodone/naloxone PR, as measured by the SF-12 physical functioning, role-physical, bodily pain, general health, vitality, and social functioning domain scores; the SF-12 physical component summary score; and the EQ-5D health status index and patient's health state assessment**
  - **In general, there was a significantly better overall outcome for the PGIC and CGIC with tapentadol PR versus oxycodone/naloxone PR, with a rating of "much improved" or "very much improved" reported for a significantly higher percentage of patients by patients and investigators, respectively**
- **In conclusion, these results suggest that tapentadol PR can be proposed as a preferred option for treating severe chronic low back pain with a neuropathic pain component**

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### Acknowledgments

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# ABSTRACT

**Purpose:** Severe chronic pain, particularly that associated with a neuropathic pain component, can have a significant negative impact on health-related quality of life. Tapentadol prolonged release (PR), a centrally acting analgesic with μ-opioid receptor agonist and noradrenaline reuptake inhibitor activities, has been shown to be effective and well tolerated for managing severe chronic low back pain with or without a neuropathic component, and has been associated with significant improvements in health-related quality of life in these patients. A fixed-dose combination of oxycodone/naloxone PR has also been shown to be effective for managing moderate to severe chronic low back pain and improving quality of life. An equianalgesic ratio of approximately 5:1 has been established for tapentadol PR versus oxycodone PR in earlier randomized, controlled trials. This study evaluated the impact of tapentadol PR and oxycodone/naloxone PR on quality of life and function measures as secondary outcomes in patients with severe chronic low back pain with a neuropathic pain component. Results for the quality of life and function measures are presented here; results for the 2 co-primary endpoints, secondary effectiveness endpoints, and safety and tolerability outcomes are presented in separate abstracts.

**Methods:** In this randomized, controlled, open-label, phase IIIb/IV study, eligible patients with severe pain (average pain intensity ≥6 on an 11-point numerical rating scale-3 [NRS-3; average 3-day pain intensity] at baseline and a rating of "positive" or "unclear" on the painDETECT questionnaire at baseline) were randomized to twice-daily tapentadol PR 50 mg or oxycodone/naloxone PR 10 mg/5 mg. After a 21-day titration period (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. Quality of life and function were evaluated using the Short Form-12 (SF-12) and EuroQol-5 Dimension (EQ-5D) questionnaires. Patients and investigators reported their impression of the overall change in a patients' condition since starting treatment on the patient global impression of change (PGIC) and clinician global impression of change (CGIC), respectively. An analysis of covariance (ANCOVA) model, including treatment and pooled centers as factors and baseline value as a covariate, was used to evaluate the SF-12 and EQ-5D in the full analysis set. The last observation carried forward (LOCF) was used for imputing missing assessments.

**Results:** With tapentadol PR (n = 130), significant improvements from baseline to final evaluation were observed in both SF-12 summary scores (least-squares [LS] mean [standard error of the mean (SEM)] change from baseline to final evaluation: physical component summary, 9.74 [0.795]; mental component summary, 3.08 [0.846]) and all domain scores (physical functioning, 8.36 [0.826]; role-physical, 7.26 [0.712]; bodily pain, 10.99 [0.946]; general health, 8.45 [0.870]; vitality, 4.94 [0.806]; social functioning, 5.25 [0.887]; role-emotional, 4.76 [0.947]; and mental health, 5.16 [0.839]; all $P < 0.001$). With oxycodone/naloxone PR (n = 125), significant improvements were observed in the SF-12 physical component summary score (LS mean [SEM] change from baseline to final evaluation, 6.20 [0.806]) and physical functioning (5.07 [0.836]), role-physical (4.67 [0.722]), bodily pain (7.46 [0.957]), general health (4.31 [0.882]), social functioning (2.29 [0.900]), role-emotional (2.59 [0.981]), and mental health (2.97 [0.858]) domain scores (all $P \leq 0.012$). Improvements in the SF-12 physical component summary score and physical functioning, role-physical, bodily pain, general health, vitality, and social functioning domain scores were significantly greater with tapentadol PR than with oxycodone/naloxone PR ($P \leq 0.017$). With tapentadol PR and oxycodone/naloxone PR, respectively, mean (standard deviation) EQ-5D health status index scores were 0.32 (0.295) and 0.34 (0.311) at baseline and 0.67 (0.317) and 0.57 (0.314) at final evaluation. EQ-5D scores improved significantly from baseline to final evaluation in both treatment groups (LS mean [SEM] change from baseline to final evaluation: tapentadol PR, 0.34 [0.028]; oxycodone/naloxone PR, 0.24 [0.028]; both $P < 0.001$), with significantly greater improvement with tapentadol PR versus oxycodone/naloxone PR ($P = 0.010$). With tapentadol PR and oxycodone/naloxone PR, respectively, ratings of "very much improved" or "much improved" were reported by 54.3% (70/129) and 29.6% (37/125) of patients on the PGIC and by 59.4% (76/128) and 35.0% (43/123) of investigators on the CGIC at final evaluation.

**Conclusions:** Tapentadol PR was associated with greater improvements in quality of life and function measures than oxycodone/naloxone PR in opioid-naive patients with severe chronic low back pain with a neuropathic pain component. The favorable effects of tapentadol PR versus oxycodone/naloxone PR on quality of life were consistently shown across different validated measures and coincided with improvements in effectiveness and tolerability outcomes (as described separately). In conclusion, tapentadol PR can be proposed as a preferred option for treating severe chronic pain with a neuropathic pain component.


# INTRODUCTION

- Neuropathic pain may have detrimental effects on health-related quality of life[1]
- Chronic low back pain is often accompanied by a neuropathic pain component, which often complicates pain management[2,3]
- Tapentadol is a centrally acting analgesic with μ-opioid receptor agonist and noradrenaline reuptake inhibitor activities[4,5]
  - Tapentadol prolonged release (PR) has been shown to be efficacious and well tolerated for managing severe chronic low back pain with or without a neuropathic component in recent phase IIIb studies[4,5]
    - In those phase IIIb studies,[4,5] tapentadol PR was also associated with significant improvements in health-related quality of life in patients with severe chronic low back pain with or without a neuropathic pain component
  - In addition, tapentadol has been shown to be effective and well tolerated for the management of moderate to severe chronic osteoarthritis knee pain,[6,7] low back pain,[7,8] pain related to diabetic peripheral neuropathy,[9] and cancer pain[10-12] with improved tolerability (particularly gastrointestinal tolerability) compared with oxycodone controlled release (CR; for osteoarthritis pain, low back pain, and cancer pain)[6-8,11] and morphine CR (for cancer pain)[10,12]

- A fixed-dose combination of oxycodone/naloxone PR has been shown to be effective and well tolerated for the management of moderate to severe chronic low back pain,[13] with better gastrointestinal tolerability compared with oxycodone PR alone[13,14]
  - The naloxone component of oxycodone/naloxone PR is an opioid antagonist that acts on the opioid receptors in the gut, reducing opioid-induced constipation by blocking the effects of oxycodone on these receptors[14]

# OBJECTIVES

- To evaluate the effects of tapentadol PR versus oxycodone/naloxone PR on quality of life and function measures in non-opioid pre-treated patients with uncontrolled, severe chronic low back pain with a neuropathic pain component
- Effectiveness, tolerability, and safety results from this study are presented separately at this congress in the following posters:
  - Effectiveness results: Baron R, et al. *Effectiveness of tapentadol prolonged release (PR) versus oxycodone/naloxone PR for severe chronic low back pain with a neuropathic pain component*
  - Tolerability and safety results: Binder A, et al. *Safety and tolerability of tapentadol prolonged release (PR) versus oxycodone/naloxone PR for severe chronic low back pain with a neuropathic pain component*

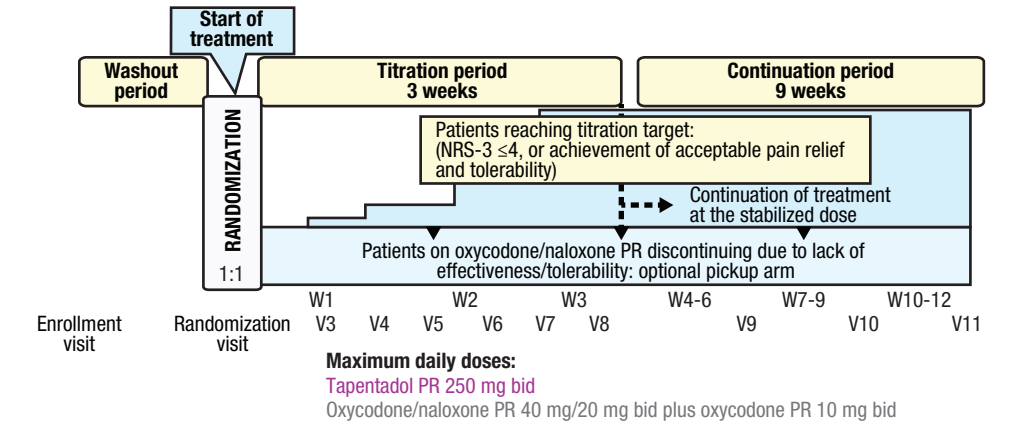
# METHODS

## *Patients*

- Key trial-specific inclusion criteria
  - Diagnosis of chronic low back pain lasting ≥3 months prior to enrollment
  - Pain requiring a strong (World Health Organization [WHO] step III) analgesic, based on the investigator's assessment at enrollment
  - Score on the painDETECT questionnaire[15] (used to evaluate the likelihood of a neuropathic pain component to low back pain; possible score of 0-38) of "positive" (score of 19-38) or "unclear" (score of 13-18) at enrollment
    - For patients taking a stable regimen of centrally acting co-analgesics, which must have been washed out prior to randomization, a "negative" painDETECT score was permitted at enrollment if that score was ≥9
    - All patients were required to have an "unclear" or "positive" painDETECT score at randomization
  - For patients not taking co-analgesics at enrollment, average pain intensity score ≥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") at enrollment
    - For patients taking co-analgesics at enrollment, which must have been washed out prior to randomization, average pain intensity score ≥5 on an 11-point NRS-3
    - All patients were required to have an average pain intensity score ≥6 on an 11-point NRS at randomization
- Key trial-specific exclusion criteria
  - Low back pain caused by cancer and/or metastatic diseases
  - Severe renal impairment or history of or current laboratory values reflecting moderate or severe hepatic impairment
  - History of seizure disorder or epilepsy; mild or moderate traumatic brain injury, stroke, transient ischemic attack, or brain neoplasm within 1 year; or severe traumatic brain injury within 15 years or residual sequelae suggesting transient changes in consciousness
  - Known or suspected paralytic ileus, acute biliary obstruction, or acute pancreatitis
- Permitted medications
  - For patients on a stable pre-study regimen of non-steroidal anti-inflammatory drugs (NSAIDs) or paracetamol, these medications were permitted at the same stable dose
  - Selective serotonin reuptake inhibitors (for the treatment of uncomplicated depression) were permitted if patients had been taking a stable dose for ≥30 days prior to the randomization visit
  - Other medications used to treat psychiatric or neurological disorders were permitted if patients had been taking a stable dose for ≥3 months prior to the randomization visit
- Prohibited medications
  - All analgesics and co-analgesics, except for study drug and stable doses of NSAIDs and paracetamol, 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 the randomization visit and during the study
  - Laxatives and antiemetics as prophylaxis were prohibited within 14 days prior to the randomization visit and during the study
  - Monoamine oxidase inhibitors were prohibited within 14 days prior to the randomization visit and during the study

## *Study Design*

- This randomized, multicenter, parallel-arm, open-label, active-controlled, phase IIIb/IV study (ClinicalTrials.gov Identifier: NCT01838616) included an optional 3- to 14-day washout period, a 3-week titration period, and a 9-week continuation period (**Figure 1**)




NRS-3, numerical rating scale-3; W, week; V, visit; PR, prolonged release.

**Figure 1. Study design.**

- During the washout period (mandatory in patients taking a centrally acting analgesic or co-analgesic at enrollment; to be completed prior to starting study treatment), centrally acting analgesics and co-analgesics were discontinued prior to the randomization visit; 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 or oxycodone/naloxone PR 10 mg/5 mg bid at minimal 3-day intervals until the minimum target of titration was reached (maximum permitted dose, tapentadol PR 250 mg bid or 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 1 of the following:
    - NRS-3 ≤4 with acceptable tolerability as reported by the patient
    - NRS-3 ≤5 if pain relief and tolerability were reported by the patient and investigator as satisfactory to continue in the study, and 1) the patient was on the maximum dose of tapentadol PR or oxycodone/naloxone PR or 2) 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 due to intolerable side effects or a lack of efficacy could be switched to tapentadol PR in a pickup arm or discontinued from the study (if they did not want to switch to tapentadol PR). The option to switch to the pickup arm due to 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*

- Quality of life was evaluated as a secondary outcome in this study using the Short Form-12 (SF-12) Health Survey and the EuroQol-5 Dimension (EQ-5D) health status questionnaire
  - The SF-12 Health Survey[16] includes 12 questions that are 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 ("lowest level of health") to 100 ("highest level of health")
  - The EQ-5D[17] health status questionnaire includes 5 dimensions of health-related quality of life (mobility, self-care, usual activities, pain or discomfort, and anxiety or depression); patients rated each dimension using a 3-point scale (1 = "no problems," 2 = "some problems," 3 = "extreme problems")
    - In addition to the 5 dimensions, a score for the patient's health state was recorded on a 0 ("worst imaginable health state") to 100 ("best imaginable health state") visual analog scale (VAS)
  - The EQ-5D health status questionnaire and SF-12 Health Survey were 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 patient global impression of change (PGIC) and clinician global impression of change (CGIC) were used to evaluate patients' global health status
  - For the PGIC, 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, investigators rated patients' global improvement and satisfaction with the treatment using the same 7-point scale as the PGIC
  - 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
- The mean daily doses of tapentadol PR and oxycodone/naloxone PR were evaluated during the titration and continuation periods
- Lumbar radiculopathy was diagnosed according to the following criteria:
  - Dermatomal pain present, radiating beyond the knee toward the foot, and evoked by stretching of the sciatic nerve, and ≥1 of the following signs of root dysfunction:
    - Sensory impairment with motor symptoms
    - And/or absent or diminished reflexes related to affected dermatome(s)
    - And/or signs of root dysfunction in quantitative sensory testing

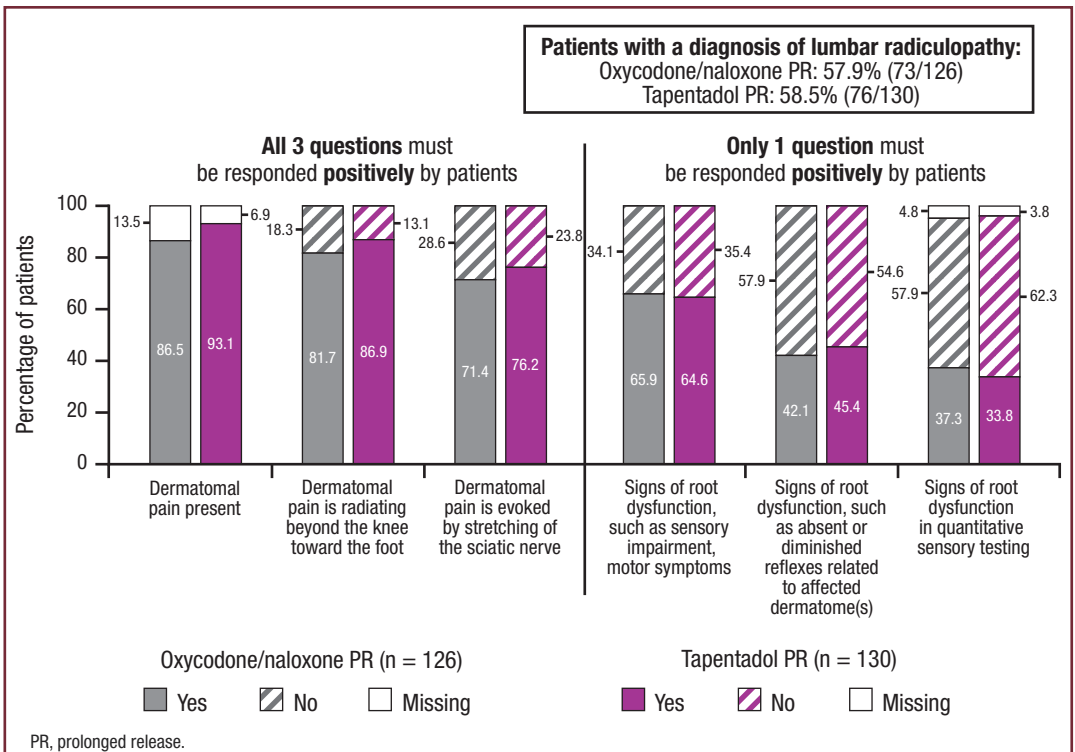
## Statistical Analyses

- This study had an adaptive 3-stage, group-sequential design (O'Brien and Fleming type design[18]); the results presented here are those of the final analysis
- A 2-sample *t* test was used for the calculation of the sample size
  - This study had 2 primary endpoints: the change in average pain intensity (11-points NRS-3) from baseline to final evaluation and the change in the Patient Assessment of Constipation Symptoms total score from baseline to final evaluation
  - For both primary endpoints, a sample size of 96 patients per group in the per-protocol set was required to show the non-inferiority of tapentadol PR as compared to 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 primary endpoints are explained in further detail in the effectiveness and tolerability and safety posters
- The safety set included all randomized patients who took ≥1 dose of study drug
- The full analysis set included all randomized patients who took ≥1 dose of study drug and had ≥1 post-baseline pain intensity assessment (NRS-3)
- The per-protocol set 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 SF-12 Health Survey, physical and mental component summary scores (possible score for each, 0 ["lowest level of health"] to 100 ["highest level of health"]) were calculated by combining scores from the 12 individual questions
- The responses to each of the EQ-5D dimensions 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 changes from baseline to final evaluation in the SF-12 domain scores and composite scores and the EQ-5D health status index score and VAS score were evaluated in the full analysis set using an analysis of covariance (ANCOVA) model including treatment and pooled centers as factors and score at baseline as a covariate
- Between-group differences in PGIC and CGIC scores were evaluated using Fisher's exact test
- The last observation carried forward (LOCF) was used for imputing missing scores
- All analyses presented in this poster were for secondary endpoints, and the respective analyses were exploratory and not adjusted for multiplicity

# RESULTS

## Patients

- The safety set included 258 patients (tapentadol PR, n = 130; oxycodone/naloxone PR, n = 128), and the full analysis set included 256 patients (tapentadol PR, n = 130; oxycodone/naloxone PR, n = 126)
- Demographic characteristics were similar in both treatment groups in the safety set
  - All patients in both treatment groups were white, and >50% were female (tapentadol PR, 59.2% [77/130]; oxycodone/naloxone PR, 65.6% [84/128])
  - The mean (standard deviation [SD]) age was 58.1 (11.48) years in the tapentadol PR group and 58.4 (12.23) years in the oxycodone/naloxone PR group
- A total of 58.5% (76/130) of patients in the tapentadol PR group and 57.9% (73/126) of patients in the oxycodone/naloxone PR group had a diagnosis of lumbar radiculopathy in the full analysis set at baseline (**Figure 2**)
- 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
- 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), respectively

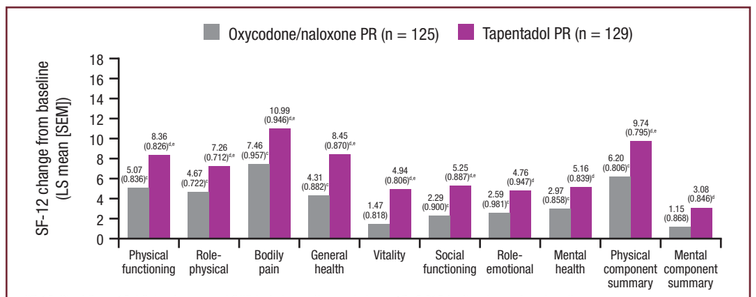



PR, prolonged release.

**Figure 2. Diagnosis of lumbar radiculopathy (full analysis set).**

## *Quality of Life and Function*

- In the tapentadol PR group of the full analysis set, significant improvements were observed in all SF-12 domain scores from baseline to final evaluation (LOCF), as well as in both SF-12 summary scores (all $P<0.001$; **Figure 3**)
  - In the oxycodone/naloxone PR group, significant improvements from baseline to final evaluation were observed in the SF-12 physical component summary score and in the SF-12 physical functioning, role-physical, bodily pain, general health, social functioning, role-emotional, and mental health domain scores (all $P \leq 0.012$; **Figure 3**)
  - The improvements observed in the tapentadol PR group from baseline to final evaluation were significantly greater than in the oxycodone/naloxone PR group for the physical component summary score and for the physical functioning, role-physical, bodily pain, general health, vitality, and social functioning domain scores (all $P \leq 0.017$; **Figure 3**)
    - At final evaluation, tapentadol PR was associated with greater improvements in the SF-12 domain and summary scores compared with oxycodone/naloxone PR, as follows (percent difference between tapentadol PR and oxycodone/naloxone PR): physical functioning, 64.8%; role-physical, 55.5%; bodily pain, 47.4%; general health, 96.0%; vitality, 236.7%; social functioning, 129.5%; role-emotional, 84.2%; mental health, 73.5%; physical component summary, 57.0%; and mental component summary, 168.5%




SF-12, Short Form-12; LS, least-squares; LOCF, last observation carried forward; PR, prolonged release; SEM, standard error of the mean; ANCOVA, analysis of covariance.
[a]Exploratory analyses.
[b]LS means and *P* values were obtained from an ANCOVA model that includes treatment and pooled centers as factors and score at randomization (baseline) as a covariate.
[c]$P \leq 0.012$ for the change from baseline.
[d]$P < 0.001$ for the change from baseline.
[e]$P \leq 0.017$ (superiority; tapentadol PR vs oxycodone/naloxone PR).

**Figure 3. Change from baseline to final evaluation in SF-12 domain and summary scores (LS mean; LOCF; full analysis set).[a,b]**

- EQ-5D health status index scores at baseline and final evaluation are shown in **Figure 4A**
  - Significant increases were observed from baseline to final evaluation (LOCF) in the EQ-5D health status index score in both treatment groups in the full analysis set (both $P<0.001$; **Figure 4B**)
  - The improvement from baseline to final evaluation in the EQ-5D health status index score was significantly greater in the tapentadol PR group than in the oxycodone/naloxone PR group ($P = 0.010$; **Figure 4B**)
- EQ-5D health state assessment scores at baseline and final evaluation are shown in **Figure 4C**
  - Significant increases were also observed from baseline to final evaluation (LOCF) in the EQ-5D health state assessment in both the tapentadol PR group and the oxycodone/naloxone PR group (both $P<0.001$; **Figure 4D**)
  - The improvement from baseline to final evaluation in the EQ-5D health state assessment was significantly greater in the tapentadol PR group than in the oxycodone/naloxone PR group ($P = 0.024$; **Figure 4D**)

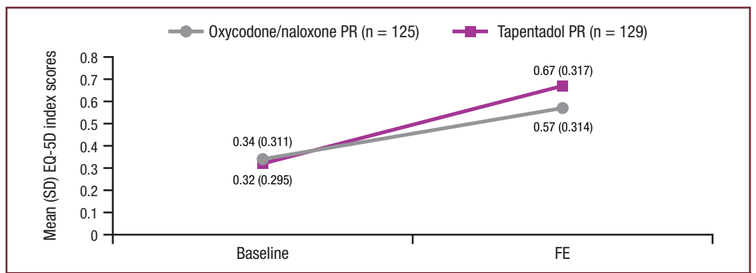



**Figure 4A. Mean (SD) EQ-5D index scores at baseline and final evaluation (LOCF; full analysis set).[a,b]**

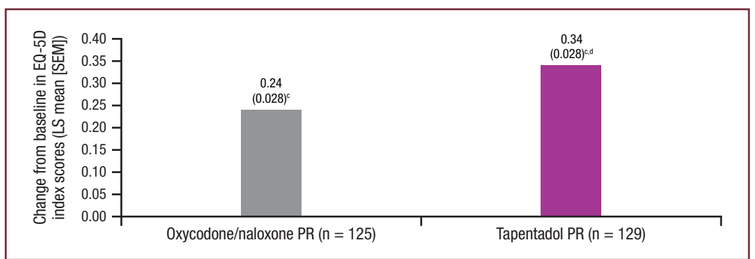



**Figure 4B. Change from baseline in EQ-5D index scores (LS mean [SEM]; LOCF; full analysis set).[a,b]**

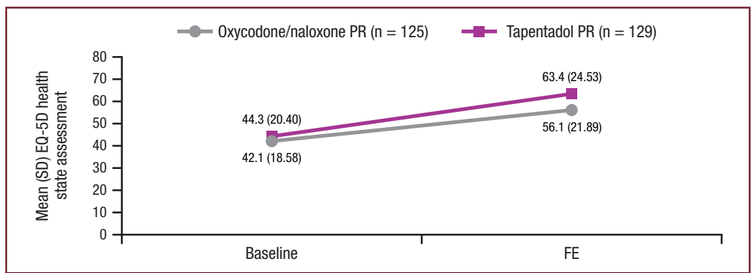



**Figure 4C. Mean (SD) EQ-5D health state assessment at baseline and final evaluation (LOCF; full analysis set).[a,b]**

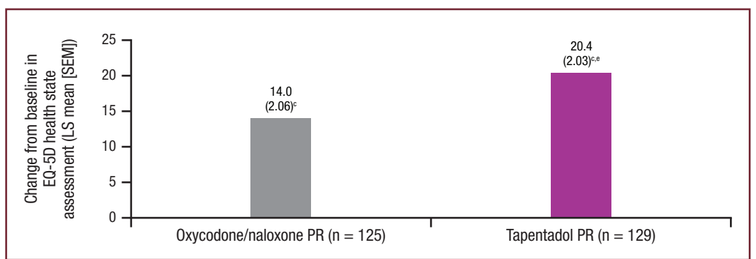



**Figure 4D. Change from baseline in EQ-5D health state assessment (LS mean [SEM]; LOCF; full analysis set).[a,b]**

SD, standard deviation; EQ-5D, EuroQol-5 Dimension; LOCF, last observation carried forward; PR, prolonged release; FE, final evaluation; LS, least-squares; SEM, standard error of the mean; ANCOVA, analysis of covariance.
[a]Exploratory analyses.
[b]LS means and *P* values are obtained from an ANCOVA model that includes treatment and pooled centers as factors and score at randomization (baseline) as a covariate.
[c]$P < 0.001$ for the change from baseline.
[d]$P = 0.010$ (superiority; tapentadol PR vs oxycodone/naloxone PR).
[e]$P = 0.024$ (superiority; tapentadol PR vs oxycodone/naloxone PR).

- 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 ($P = 0.0031$; LOCF; **Figures 5A** and **5B**)
  - Overall, based on PGIC results, most patients 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 ($P = 0.005$)

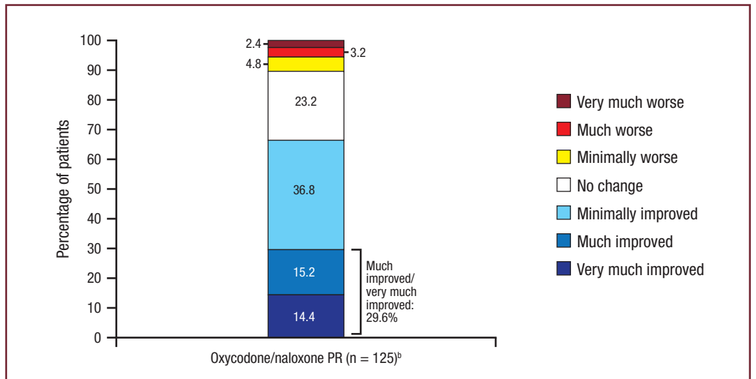



**Figure 5A. PGIC ratings at final evaluation for oxycodone/naloxone PR (LOCF; full analysis set).[a]**

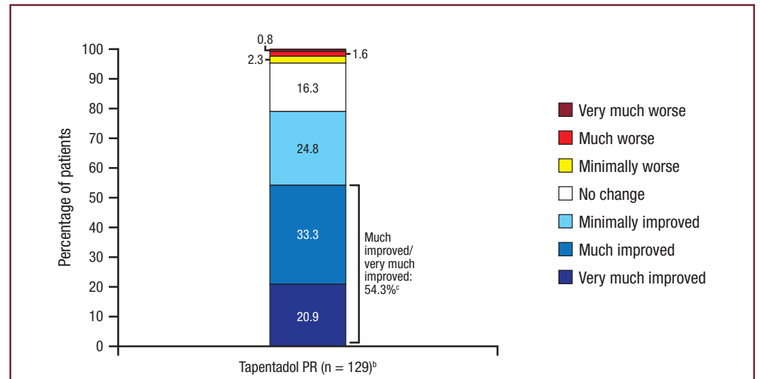



**Figure 5B. PGIC ratings at final evaluation for tapentadol PR (LOCF; full analysis set).[a]**

PGIC, patient global impression of change; PR, prolonged release; LOCF, last observation carried forward.
[a]Exploratory analyses.
[b]n values are the numbers of patients with PGIC results available for final evaluation.
[c]$P = 0.0031$ vs oxycodone/naloxone PR.

- 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 ($P = 0.0022$; LOCF; **Figures 6A** and **6B**)
  - Overall, based on CGIC results, investigators rated patients' conditions more favorably at final evaluation with tapentadol PR than with oxycodone/naloxone PR ($P = 0.005$)

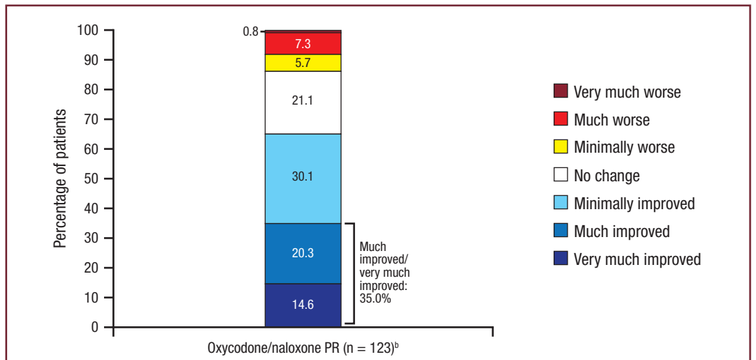



**Figure 6A. CGIC ratings at final evaluation for oxycodone/naloxone PR (LOCF; full analysis set).[a]**

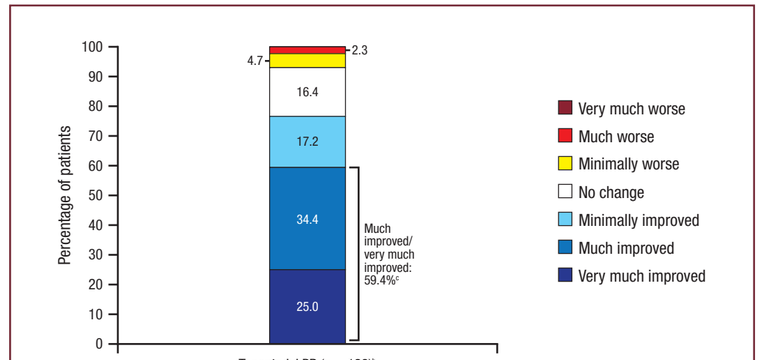



**Figure 6B. CGIC ratings at final evaluation for tapentadol PR (LOCF; full analysis set).[a]**

CGIC, clinician global impression of change; PR, prolonged release; LOCF, last observation carried forward.
[a]Exploratory analyses.
[b]n values are the numbers of patients with CGIC results available for final evaluation.
[c]$P = 0.0022$ vs oxycodone/naloxone PR.

## CONCLUSIONS

- **Tapentadol PR was associated with greater improvements in quality of life and function measures versus oxycodone/naloxone PR in non-opioid pre-treated patients with severe chronic low back pain with a neuropathic pain component**
- **The favorable effects of tapentadol PR versus oxycodone/naloxone PR on quality of life were consistently shown across different validated measures (including SF-12, EQ-5D, PGIC, and CGIC) and coincided with improvements in effectiveness and tolerability outcomes (as described separately)**
  - **Tapentadol PR was associated with significantly improved quality of life and function compared with oxycodone/naloxone PR, as measured by the SF-12 physical functioning, role-physical, bodily pain, general health, vitality, and social functioning domain scores; the SF-12 physical component summary score; and the EQ-5D health status index and patient's health state assessment**
  - **In general, there was a significantly better overall outcome for the PGIC and CGIC with tapentadol PR versus oxycodone/naloxone PR, with a rating of "much improved" or "very much improved" reported for a significantly higher percentage of patients by patients and investigators, respectively**
- **In conclusion, these results suggest that tapentadol PR can be proposed as a preferred option for treating severe chronic low back pain with a neuropathic pain component**

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