Effectiveness of Tapentadol Prolonged Release (PR) Versus Oxycodone/Naloxone PR for Severe Chronic Low Back Pain With a Neuropathic Pain Component

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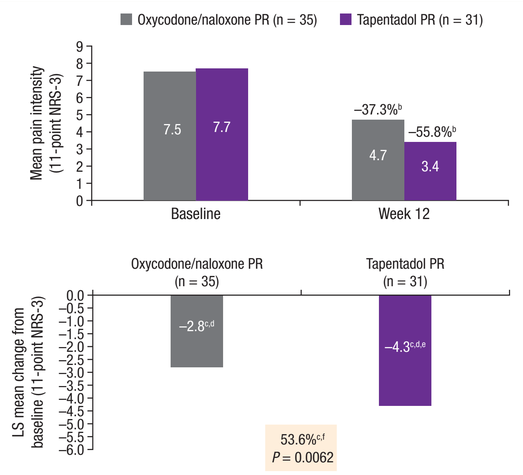
ABSTRACT

Aims: **To evaluate the effectiveness of tapentadol prolonged release (PR) versus oxycodone/naloxone PR, including effects on neuropathic pain.**

Methods: **In this ongoing, open-label, phase 3b/4 study, eligible patients (average pain intensity [numerical rating scale-3] ≥6 and painDETECT "positive" or "unclear" ratings) are randomized to twice-daily tapentadol PR 50 mg or oxycodone/naloxone PR 10 mg/5 mg. After 21 days of titration (maximum twice-daily doses: tapentadol PR 250 mg or oxycodone/naloxone PR 40 mg/ 20 mg plus oxycodone PR 10 mg), target doses are continued for 9 weeks. The primary efficacy endpoint is the change in NRS-3 from baseline (randomization) to final evaluation. PainDETECT and Neuropathic Pain Symptom Inventory (NPSI) questionnaires evaluated effects on neuropathic pain-related symptoms. Interim results are presented (77/240 [32.1%] planned patients).**

Results: **In this interim subset, for the primary efficacy endpoint, the effectiveness of tapentadol PR was non-inferior, and even superior, to oxycodone/naloxone PR (least-squares mean difference [97.5% confidence interval], –1.5 [–2.9,–0.2]; descriptive analysis; Figure 1). Improvements in painDETECT and NPSI scores were significantly greater with tapentadol PR versus oxycodone/naloxone PR ($P \leq 0.01$; Table 1).**

Conclusions: **For tapentadol PR, results indicate superior effectiveness and greater improvements in neuropathic pain-related symptoms versus oxycodone/naloxone PR.**



LS, least-squares; LOCF, last observation carried forward; PR, prolonged release; NRS-3, numerical rating scale-3.
[a]Descriptive analyses.
[b]Percent difference from baseline.
[c]LS means and *P* values are obtained from an analysis of covariance model that includes treatment and pooled centers as factors and score at randomization (baseline) as a covariate.
[d]$P < 0.001$ for the change from baseline.
[e]$P < 0.001$ (non-inferiority; tapentadol PR vs oxycodone/naloxone PR).
[f]Percent difference between tapentadol PR and oxycodone/naloxone PR, using oxycodone/naloxone PR as the base (denominator). Fifty-four percent more pain reduction was observed from baseline to final evaluation with tapentadol PR than with oxycodone/naloxone PR.

Figure 1. Mean pain intensity at baseline and Week 12 and change in pain intensity from baseline to final evaluation (LS mean; LOCF; per protocol set).[a]

Table 1. Total painDETECT Scores and NPSI Subscores (LOCF; Full Analysis Set)

Score	Tapentadol PR (n = 38)	Oxycodone/naloxone PR (n = 39)
Total painDETECT score		
Mean (SD) score at baseline	20.7 (4.88)	22.3 (4.78)
Mean (SD) changes from baseline (LS mean)	–10.5 (1.15)[a,b]	–6.0 (1.20)[a]
NPSI subscores, mean changes from baseline to final evaluation		
Burning pain	–0.43[a,c]	–0.23[a]
Pressing pain	–0.35[a,c]	–0.19[a]
Paroxysmal pain	–0.39[a,c]	–0.18[a]
Evoked pain	–0.34[a,c]	–0.18[a]
Paresthesia/dysesthesia	–0.36[a,c]	–0.19[a]

NPSI, Neuropathic Pain Symptom Inventory; LOCF, last observation carried forward; PR, prolonged release; SD, standard deviation; LS, least-squares.
[a]$P < 0.001$ for the change from baseline.
[b]$P = 0.010$ versus oxycodone/naloxone PR, in favor of tapentadol PR.
[c]$P \leq 0.003$ versus oxycodone/naloxone PR, in favor of tapentadol PR.

INTRODUCTION

- Chronic low back pain is often associated with a neuropathic pain component that may complicate pain management[1]
- Tapentadol prolonged release (PR) is a centrally acting analgesic with μ-opioid receptor agonist and noradrenaline reuptake inhibitor activities[2,3]
  - Tapentadol PR has been shown to be effective for the management of moderate to severe, chronic osteoarthritis knee pain,[4,5] low back pain,[5,6] pain related to diabetic peripheral neuropathy,[7] and cancer pain[8] with improved tolerability (particularly gastrointestinal tolerability) compared with oxycodone PR (for osteoarthritis and low back pain)[4-6] and morphine controlled release (for cancer pain)[8]
  - In recent phase 3b studies,[9,10] tapentadol PR has also been shown to be effective and well tolerated for the management of severe, chronic low back pain with or without a neuropathic component
- Fixed-dose combinations of oxycodone/naloxone PR have also been shown to be effective and well tolerated for the management of moderate to severe, chronic low back pain,[11] with better gastrointestinal tolerability compared with oxycodone PR alone[11,12]
  - 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[12]

OBJECTIVES

- To evaluate the effectiveness of tapentadol PR versus oxycodone/naloxone PR in non-opioid, pre-treated patients with uncontrolled, severe, chronic low back pain with a neuropathic pain component
- To evaluate the effects of tapentadol PR versus oxycodone/naloxone PR on neuropathic pain-related symptoms
- Tolerability and safety results from this study are presented in poster **<<XX>>**, and quality of life and function outcomes from this study are presented in poster **<<XX>>**

<<Poster numbers will be added upon receipt>>

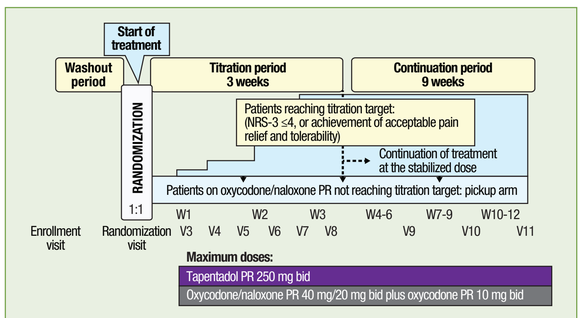
METHODS

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[13] (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 be washed out prior to randomization, a "negative" painDETECT score is permitted at enrollment if that score is ≥9
  - For patients taking co-analgesics at enrollment, which must be washed out prior to randomization, average pain intensity score ≥5 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 who are not taking co-analgesics at enrollment, average pain intensity score ≥6 on an 11-point NRS-3 at enrollment
- 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, non-steroidal anti-inflammatory drugs (NSAIDs) or paracetamol are permitted at the same stable dose
  - Selective serotonin reuptake inhibitors (for the treatment of uncomplicated depression) are permitted if patients have been taking a stable dose for ≥30 days prior to the randomization visit
  - Other medications used to treat psychiatric or neurological disorders are permitted if patients have 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, are prohibited during the study (after the washout period)
    - WHO Step II and III analgesics, except for study drug, are prohibited within 30 days prior to enrollment and during the study
  - Laxatives and antiemetics as prophylaxis are prohibited within 14 days of enrollment and during the study
  - Monoamine oxidase inhibitors are prohibited within 14 days prior to enrollment and during the study

Study Design

- This on-going, randomized, multicenter, parallel-arm, open-label, active-controlled, phase 3b/4 study (ClinicalTrials.gov Identifier: NCT01838616) includes an optional 3- to 14-day washout period, a 3-week titration period, and a 9-week continuation period (**Figure 2**)



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

Figure 2. Study design.

- During the optional washout period (prior to starting study treatment), centrally acting analgesics and co-analgesics are discontinued prior to the randomization visit; the duration of the washout period is individualized depending on the type and dose of the previous co-analgesics
- At the randomization visit, patients are 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 can 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 is 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 is defined as one of the following:
    - NRS-3 ≤4 with acceptable tolerability, as reported by the patient
    - NRS-3 of ≤5 if pain relief and tolerability are reported as satisfactory by the patient and investigator to continue in the study and 1) the patient is on the maximum dose of tapentadol PR, or oxycodone/naloxone PR, or 2) the maximum daily dose cannot be achieved because of side effects
- Patients who reach the minimum target of titration are eligible to enter a 9-week continuation period, during which patients continue on the same stable dose of study drug; for patients not taking the maximum dose, a single titration using the same increments as during titration is permitted during the continuation period
  - Patients in the tapentadol PR group who do not reach the minimum target of titration by the end of the titration period are discontinued from the study
  - Patients in the oxycodone/naloxone PR group who do not reach the minimum target of titration by the end of the titration period can be switched to tapentadol PR in a pickup arm or discontinued from the study (if they do not want to switch to tapentadol PR)

Study Evaluations

- Patients rate their average pain intensity during the past 3 days on an 11-point NRS at each study visit
- The primary effectiveness endpoint is the change in average pain intensity during the last 3 days (NRS-3) from the randomization visit (baseline) to final evaluation at the end of the continuation period in the per protocol set (defined below)
- Changes in neuropathic pain symptoms based on the painDETECT questionnaire and the Neuropathic Pain Symptom Inventory (NPSI) are evaluated as secondary endpoints
  - The painDETECT questionnaire[13] is completed at the enrollment visit, the randomization visit, at the end of titration (Visit 8), and at the final evaluation visit
    - The painDETECT questionnaire,[13] a patient-reported assessment validated for both screening and control, includes 7 questions addressing the frequency and quality of neuropathic pain symptoms (scored from 0-5; 0 = "never" to 5 = "very strongly"), 1 question addressing pain patterns over time, and 1 question evaluating radiating pain
  - The NPSI[14] is completed at the enrollment visit, 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 NPSI[14] is a validated measure that includes 10 items 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 mean daily doses of tapentadol PR and oxycodone/naloxone PR were evaluated at the end of titration

Statistical Analyses

- This study has an adaptive 3-stage group-sequential design (O'Brien and Fleming type design[15]), with 1 planned interim analysis after observation of one-third of the total planned study population, the results of which are presented here
- A 2-sample *t* test was used for the calculation of the sample size. The sample size computation for the primary effectiveness endpoint was based on a standard deviation (SD) of 2.5 for the change in pain intensity from baseline and a non-inferiority margin of 1.3; the sample size computation for the second endpoint was based on a SD of 1.0 for the change from baseline in the Patient Assessment of Constipation Symptoms (PAC-SYM) total score, an expected difference of 0.1 in the change from baseline in the PAC-SYM total score in favor of oxycodone/naloxone PR, and a non-inferiority margin of 0.7
  - For both endpoints, a sample size of 96 patients per group in the per protocol set (defined below) is 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 are available for the per protocol set, a total of 240 patients should receive study treatment in the overall study
  - Statistical methods for the second primary endpoint are explained in further detail in poster **<<XX>>** ***<<Poster number will be added upon receipt>>***
- For the final analysis of the primary effectiveness endpoint, tapentadol immediate release is considered to be non-inferior to oxycodone/naloxone PR if the upper limit of the 2-sided 97.5% repeated confidence interval (RCI) for the treatment difference (tapentadol PR minus oxycodone/naloxone PR) is less than the non-inferiority margin of 1.3
  - For this interim analysis, the test statistics of the normal inverse method were used to demonstrate non-inferiority (as described below)
- The safety set includes all randomized patients who took ≥1 dose of study drug
- The full analysis set includes all randomized patients who took ≥1 dose of study drug and had ≥1 post-baseline pain intensity assessment (NRS-3)
- The per protocol set is a subpopulation of the full analysis set that includes all patients who had no major protocol deviations that could impact the primary outcomes of the study
- The main analysis for the primary efficacy endpoint is adjusted for the group-sequential design and multiplicity, guaranteeing overall control of type I error rate (2.5% one-sided)
  - These results are based on the inverse normal method,[16] and those test statistics are shown in the current poster and compared to the appropriate critical value for the primary efficacy endpoint (3.935)
- All other analyses are exploratory, and all *P* values shown are descriptive *P* values
- For the painDETECT questionnaire, scores for the 9 individual questions are summed to yield a total painDETECT score (possible score, 0-38)
- For the NPSI, scores for the 10 individual items evaluating the properties of neuropathic pain are averaged and divided by 10 to yield 5 subscores (each with a possible score of 0-1): 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 are also summed and divided by 100 to yield an overall feeling score (possible score, 0-1)
- The changes from baseline to final evaluation in pain intensity (NRS-3; primary endpoint), the total painDETECT score, and the NPSI subscores and overall feeling score are evaluated using an analysis of covariance model including treatment and pooled center as factors and score at baseline as a covariate
  - The last observation carried forward (LOCF) is used for imputing missing scores
  - The patients who entered the pickup arm were treated as discontinuations using the LOCF. The pickup arm was not analyzed during this interim analysis

RESULTS

Patients and Dosing

- For this interim analysis, 77 patients (tapentadol PR, n = 38; oxycodone/naloxone PR, n = 39) were included in the safety set and in the full analysis set, and 66 patients (tapentadol PR, n = 31; oxycodone/naloxone PR, n = 35) were included in the per protocol set
- Demographic characteristics were comparable between treatment groups in the safety set (Table 2)

Table 2. Demographics and Study Population (Safety Set)

Characteristic	Tapentadol PR (n = 38)	Oxycodone/naloxone PR (n = 39)
Mean (SD) age, years	55.8 (12.33)	58.7 (11.76)
Gender, n (%)		
Female	24 (63.2)	22 (56.4)
Male	14 (36.8)	17 (43.6)
Mean (SD) BMI, kg/m²	29.6 (5.85)	28.7 (5.53)
Race, n (%)		
White	38 (100.0)	39 (100.0)

PR, prolonged release; SD, standard deviation; BMI, body mass index.

- A total of 76.3% (29/38) patients in the tapentadol PR group, and 76.9% (30/39) of patients in the oxycodone/naloxone PR group had a diagnosis of lumbar radiculopathy at baseline
- During the titration period, 10.5% (4/38) of patients in the tapentadol PR group and 46.2% (18/39) of patients in the oxycodone/naloxone PR group discontinued the study, while during the overall treatment period, 21.1% (8/38) of patients in the tapentadol PR group and 59.0% (23/39) of patients in the oxycodone/naloxone PR group discontinued the study
  - The most common reasons for treatment discontinuation during the overall study were adverse events and a lack of efficacy
  - In the tapentadol PR and oxycodone/naloxone PR groups, respectively, adverse events led to discontinuation in 5.3% (2/38) and 30.8% (12/39) of patients during the titration period and in 10.5% (4/38) and 33.3% (13/39) of patients during the overall treatment period, while a lack of efficacy led to discontinuation in 0% and 7.7% (3/39) of patients during the titration period and in 0% and 12.8% (5/39) of patients during the overall treatment period
- In the tapentadol PR and oxycodone/naloxone PR groups, respectively, 79% (30/38) and 41% (16/39) of patients in the safety set completed study treatment
  - Overall, 92% more patients stayed on tapentadol PR treatment compared with oxycodone/naloxone PR treatment
- At the end of titration, the mean SD daily doses were **<<X.XX>>** mg/day in the tapentadol PR group and **<<X.XX>>** mg/day in the oxycodone/naloxone PR group

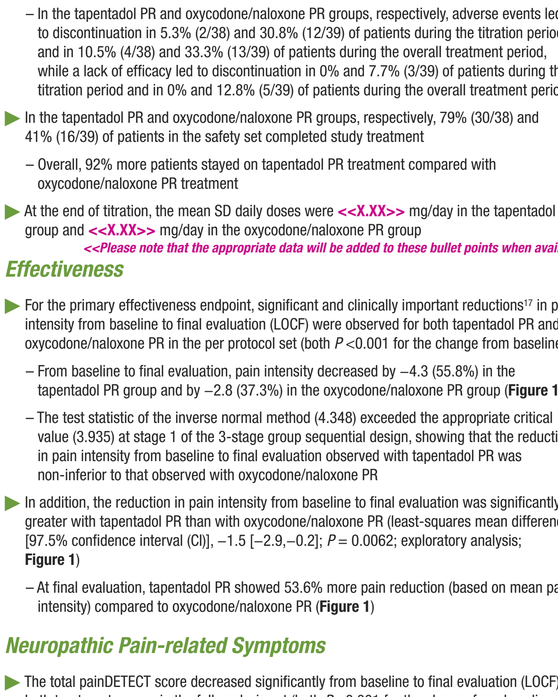
<<Please note that the appropriate data will be added to these bullet points when available>>

Effectiveness

- For the primary effectiveness endpoint, significant and clinically important reductions[17] in pain intensity from baseline to final evaluation (LOCF) were observed for both tapentadol PR and oxycodone/naloxone PR in the per protocol set (both $P < 0.001$ for the change from baseline)
  - From baseline to final evaluation, pain intensity decreased by –4.3 (55.8%) in the tapentadol PR group and by –2.8 (37.3%) in the oxycodone/naloxone PR group (**Figure 1**)
  - The test statistic of the inverse normal method (4.348) exceeded the appropriate critical value (3.935) at stage 1 of the 3-stage group sequential design, showing that the reduction in pain intensity from baseline to final evaluation observed with tapentadol PR was non-inferior to that observed with oxycodone/naloxone PR
- In addition, the reduction in pain intensity from baseline to final evaluation was significantly greater with tapentadol PR than with oxycodone/naloxone PR (least-squares mean difference [97.5% confidence interval (CI)], –1.5 [–2.9,–0.2]; $P = 0.0062$; exploratory analysis; **Figure 1**)
  - At final evaluation, tapentadol PR showed 53.6% more pain reduction (based on mean pain intensity) compared to oxycodone/naloxone PR (**Figure 1**)

Neuropathic Pain-related Symptoms

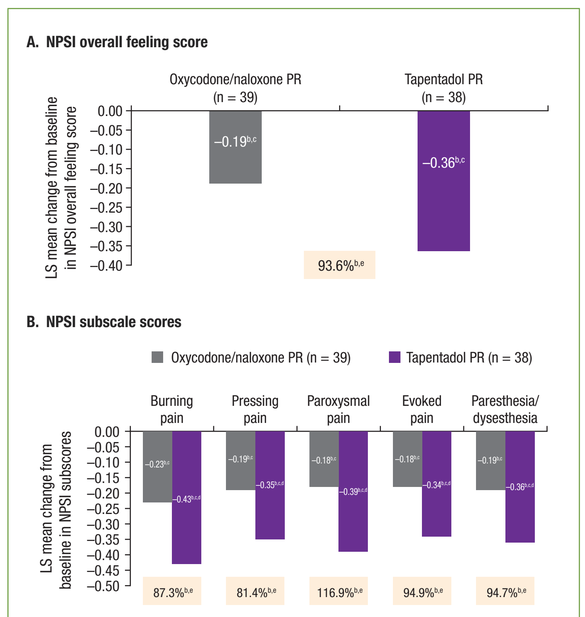
- The total painDETECT score decreased significantly from baseline to final evaluation (LOCF) in both treatment groups in the full analysis set (both $P < 0.001$ for the change from baseline; **Table 1** and **Figure 3**)
- From baseline to final evaluation, the total painDETECT score decreased by –10.5 (46.4%) in the tapentadol PR group and by –6.0 (27.8%) in the oxycodone/naloxone PR group
- The decrease in the total painDETECT score from baseline to final evaluation was significantly greater in the tapentadol PR group than in the oxycodone/naloxone PR group (least-squares mean difference [95% CI], –4.5 [–7.9, –1.1]; $P = 0.010$)
  - At final evaluation, the painDETECT score was reduced by 75% more in the tapentadol PR than in the oxycodone/naloxone PR



LS, least-squares; LOCF, last observation carried forward; PR, prolonged release.
[a]Descriptive analyses.
[b]Percent difference from baseline.
[c]LS means and *P* values are obtained from an analysis of covariance model that includes treatment and pooled centers as factors and score at randomization (baseline) as a covariate.
[d]$P < 0.001$ for the change from baseline.
[e]$P = 0.01$ (superiority; tapentadol PR vs oxycodone/naloxone PR).
[f]Percent difference between tapentadol PR and oxycodone/naloxone PR, using oxycodone/naloxone PR as the base (denominator).

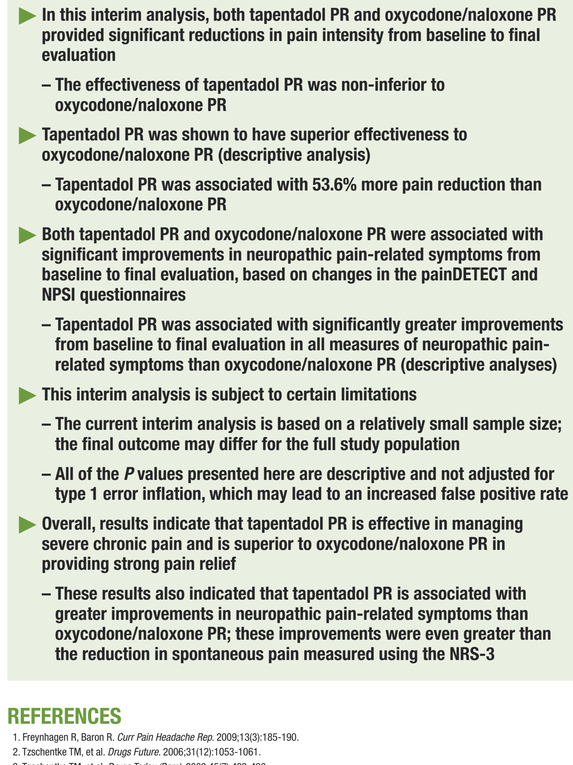
Figure 3. Mean total painDETECT score at baseline and Week 12 and change in the total painDETECT score from baseline to final evaluation (LS mean; LOCF; full analysis set).[a]

- The NPSI overall feeling score decreased significantly from baseline to final evaluation in the tapentadol PR group and the oxycodone/naloxone PR group (both $P < 0.001$; **Figure 4A**)
  - The NPSI overall feeling score decreased by 93.6% more in the tapentadol PR group than in the oxycodone/naloxone PR group (**Figure 4A**)
- A significant decrease from baseline to final evaluation (LOCF) was also observed in the NPSI subscores in both treatment groups in the full analysis set (all $P < 0.001$ for the change from baseline; **Table 1**, **Figure 4B**, and **Figure 5**)
  - The improvements in all NPSI subscores were significantly greater in the tapentadol PR group than in the oxycodone/naloxone PR group (all $P \leq 0.003$; **Figure 4A**)
    - NPSI subscores decreased from baseline to final evaluation by 81.4% to 116.9% more with tapentadol PR than with oxycodone/naloxone PR (**Figure 4B**)



NPSI, Neuropathic Pain Symptom Inventory; LS, least-squares; LOCF, last observation carried forward; PR, prolonged release.
[a]Descriptive analyses.
[b]LS means and *P* values are obtained from an analysis of covariance 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]$P \leq 0.003$ (superiority; tapentadol PR vs oxycodone/naloxone PR).
[e]Percent difference between tapentadol PR and oxycodone/naloxone PR, using oxycodone/naloxone PR as the base (denominator).

Figure 4. Changes from baseline to final evaluation in the NPSI A) overall feeling score and B) subscale scores (LS mean; LOCF; full analysis set).[a]



NPSI, Neuropathic Pain Symptom Inventory; LOCF, last observation carried forward; PR, prolonged release.

Figure 5. Mean NPSI subscores at baseline and Week 12 (LOCF; full analysis set).

CONCLUSIONS

- **In this interim analysis, both tapentadol PR and oxycodone/naloxone PR provided significant reductions in pain intensity from baseline to final evaluation**
  - **The effectiveness of tapentadol PR was non-inferior to oxycodone/naloxone PR**
- **Tapentadol PR was shown to have superior effectiveness to oxycodone/naloxone PR (descriptive analysis)**
  - **Tapentadol PR was associated with 53.6% more pain reduction than oxycodone/naloxone PR**
- **Both tapentadol PR and oxycodone/naloxone PR were associated with significant improvements in neuropathic pain-related symptoms from baseline to final evaluation, based on changes in the painDETECT and NPSI questionnaires**
  - **Tapentadol PR was associated with significantly greater improvements from baseline to final evaluation in all measures of neuropathic pain-related symptoms than oxycodone/naloxone PR (descriptive analyses)**
- **This interim analysis is subject to certain limitations**
  - **The current interim analysis is based on a relatively small sample size; the final outcome may differ for the full study population**
  - **All of the *P* values presented here are descriptive and not adjusted for type 1 error inflation, which may lead to an increased false positive rate**
- **Overall, results indicate that tapentadol PR is effective in managing severe chronic pain and is superior to oxycodone/naloxone PR in providing strong pain relief**
  - **These results also indicated that tapentadol PR is associated with greater improvements in neuropathic pain-related symptoms than oxycodone/naloxone PR; these improvements were even greater than the reduction in spontaneous pain measured using the NRS-3**

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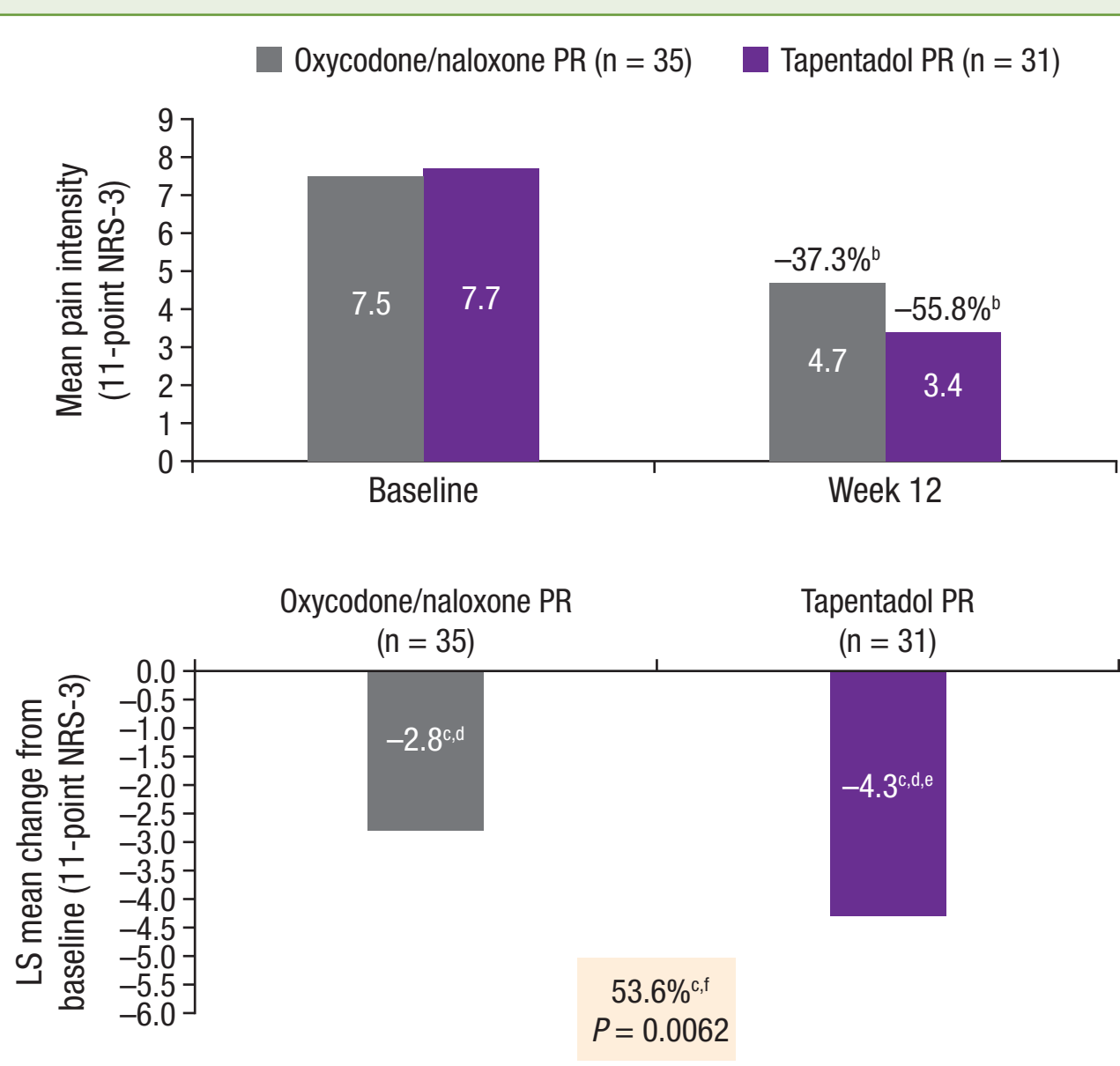
ABSTRACT

Aims: To evaluate the effectiveness of tapentadol prolonged release (PR) versus oxycodone/naloxone PR, including effects on neuropathic pain.

Methods: In this ongoing, open-label, phase 3b/4 study, eligible patients (average pain intensity [numerical rating scale-3] ≥6 and painDETECT "positive" or "unclear" ratings) are randomized to twice-daily tapentadol PR 50 mg or oxycodone/naloxone PR 10 mg/5 mg. After 21 days of titration (maximum twice-daily doses: tapentadol PR 250 mg or oxycodone/naloxone PR 40 mg/20 mg plus oxycodone PR 10 mg), target doses are continued for 9 weeks. The primary efficacy endpoint is the change in NRS-3 from baseline (randomization) to final evaluation. PainDETECT and Neuropathic Pain Symptom Inventory (NPSI) questionnaires evaluated effects on neuropathic pain-related symptoms. Interim results are presented (77/240 [32.1%] planned patients).

Results: In this interim subset, for the primary efficacy endpoint, the effectiveness of tapentadol PR was non-inferior, and even superior, to oxycodone/naloxone PR (least-squares mean difference [97.5% confidence interval], –1.5 [–2.9,–0.2]; descriptive analysis; Figure 1). Improvements in painDETECT and NPSI scores were significantly greater with tapentadol PR versus oxycodone/naloxone PR ($P \leq 0.01$; Table 1).

Conclusions: For tapentadol PR, results indicate superior effectiveness and greater improvements in neuropathic pain-related symptoms versus oxycodone/naloxone PR.



LS, least-squares; LOCF, last observation carried forward; PR, prolonged release; NRS-3, numerical rating scale-3.
[a]Descriptive analyses.
[b]Percent difference from baseline.
[c]LS means and *P* values are obtained from an analysis of covariance model that includes treatment and pooled centers as factors and score at randomization (baseline) as a covariate.
[d]$P < 0.001$ for the change from baseline.
[e]$P < 0.001$ (non-inferiority; tapentadol PR vs oxycodone/naloxone PR).
[f]Percent difference between tapentadol PR and oxycodone/naloxone PR, using oxycodone/naloxone PR as the base (denominator). Fifty-four percent more pain reduction was observed from baseline to final evaluation with tapentadol PR than with oxycodone/naloxone PR.

Figure 1. Mean pain intensity at baseline and Week 12 and change in pain intensity from baseline to final evaluation (LS mean; LOCF; per protocol set).[a]

Table 1. Total painDETECT Scores and NPSI Subscores (LOCF; Full Analysis Set)

Score	Tapentadol PR (n = 38)	Oxycodone/naloxone PR (n = 39)
Total painDETECT score		
Mean (SD) score at baseline	20.7 (4.88)	22.3 (4.78)
Mean (SD) changes from baseline (LS mean)	–10.5 (1.15)[a,b]	–6.0 (1.20)[a]
NPSI subscores, mean changes from baseline to final evaluation		
Burning pain	–0.43[a,c]	–0.23[a]
Pressing pain	–0.35[a,c]	–0.19[a]
Paroxysmal pain	–0.39[a,c]	–0.18[a]
Evoked pain	–0.34[a,c]	–0.18[a]
Paresthesia/dysesthesia	–0.36[a,c]	–0.19[a]

NPSI, Neuropathic Pain Symptom Inventory; LOCF, last observation carried forward; PR, prolonged release; SD, standard deviation; LS, least-squares.
[a]$P < 0.001$ for the change from baseline.
[b]$P = 0.010$ versus oxycodone/naloxone PR, in favor of tapentadol PR.
[c]$P \leq 0.003$ versus oxycodone/naloxone PR, in favor of tapentadol PR.

INTRODUCTION

- Chronic low back pain is often associated with a neuropathic pain component that may complicate pain management[1]
- Tapentadol prolonged release (PR) is a centrally acting analgesic with μ-opioid receptor agonist and noradrenaline reuptake inhibitor activities[2,3]
  - Tapentadol PR has been shown to be effective for the management of moderate to severe, chronic osteoarthritis knee pain,[4,5] low back pain,[5,6] pain related to diabetic peripheral neuropathy,[7] and cancer pain[8] with improved tolerability (particularly gastrointestinal tolerability) compared with oxycodone PR (for osteoarthritis and low back pain)[4-6] and morphine controlled release (for cancer pain)[8]
  - In recent phase 3b studies,[9,10] tapentadol PR has also been shown to be effective and well tolerated for the management of severe, chronic low back pain with or without a neuropathic component
- Fixed-dose combinations of oxycodone/naloxone PR have also been shown to be effective and well tolerated for the management of moderate to severe, chronic low back pain,[11] with better gastrointestinal tolerability compared with oxycodone PR alone[11,12]
  - 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[12]

OBJECTIVES

- To evaluate the effectiveness of tapentadol PR versus oxycodone/naloxone PR in non-opioid, pre-treated patients with uncontrolled, severe, chronic low back pain with a neuropathic pain component
- To evaluate the effects of tapentadol PR versus oxycodone/naloxone PR on neuropathic pain-related symptoms
- Tolerability and safety results from this study are presented in poster **<<XX>>**, and quality of life and function outcomes from this study are presented in poster **<<XX>>**

<<Poster numbers will be added upon receipt>>

METHODS

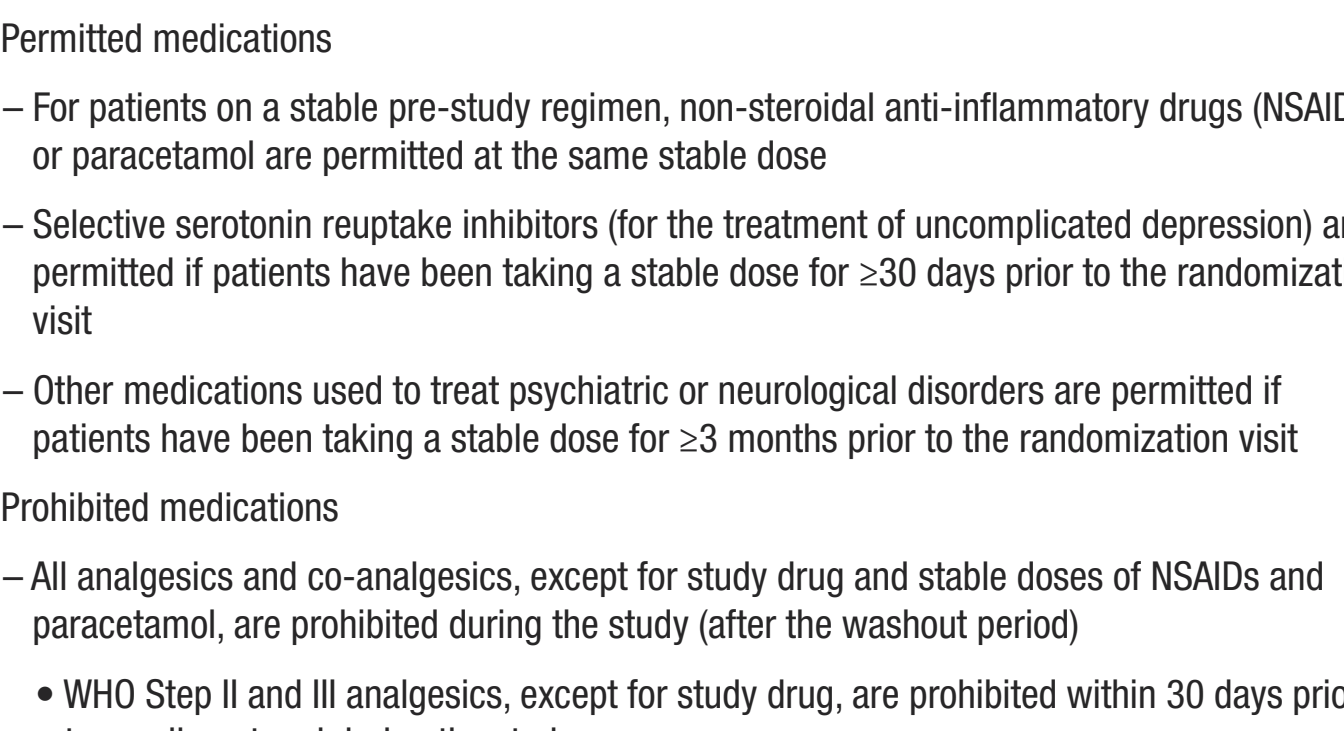
Patients

- 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[13] (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 be washed out prior to randomization, a "negative" painDETECT score is permitted at enrollment if that score is ≥9
  - For patients taking co-analgesics at enrollment, which must be washed out prior to randomization, average pain intensity score ≥5 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 who are not taking co-analgesics at enrollment, average pain intensity score ≥6 on an 11-point NRS-3 at enrollment

- 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, non-steroidal anti-inflammatory drugs (NSAIDs) or paracetamol are permitted at the same stable dose
  - Selective serotonin reuptake inhibitors (for the treatment of uncomplicated depression) are permitted if patients have been taking a stable dose for ≥30 days prior to the randomization visit
  - Other medications used to treat psychiatric or neurological disorders are permitted if patients have 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, are prohibited during the study (after the washout period)
    - WHO Step II and III analgesics, except for study drug, are prohibited within 30 days prior to enrollment and during the study
  - Laxatives and antiemetics as prophylaxis are prohibited within 14 days of enrollment and during the study
  - Monoamine oxidase inhibitors are prohibited within 14 days prior to enrollment and during the study

Study Design

- This on-going, randomized, multicenter, parallel-arm, open-label, active-controlled, phase 3b/4 study (ClinicalTrials.gov Identifier: NCT01838616) includes an optional 3- to 14-day washout period, a 3-week titration period, and a 9-week continuation period (**Figure 2**)



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

Figure 2. Study design.

- During the optional washout period (prior to starting study treatment), centrally acting analgesics and co-analgesics are discontinued prior to the randomization visit; the duration of the washout period is individualized depending on the type and dose of the previous co-analgesics
- At the randomization visit, patients are 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 can 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 is 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 is defined as one of the following:
    - NRS-3 ≤4 with acceptable tolerability, as reported by the patient
    - NRS-3 of ≤5 if pain relief and tolerability are reported as satisfactory by the patient and investigator to continue in the study and 1) the patient is on the maximum dose of tapentadol PR, or oxycodone/naloxone PR, or 2) the maximum daily dose cannot be achieved because of side effects
- Patients who reach the minimum target of titration are eligible to enter a 9-week continuation period, during which patients continue on the same stable dose of study drug; for patients not taking the maximum dose, a single titration using the same increments as during titration is permitted during the continuation period
  - Patients in the tapentadol PR group who do not reach the minimum target of titration by the end of the titration period are discontinued from the study
  - Patients in the oxycodone/naloxone PR group who do not reach the minimum target of titration by the end of the titration period can be switched to tapentadol PR in a pickup arm or discontinued from the study (if they do not want to switch to tapentadol PR)

Study Evaluations

- Patients rate their average pain intensity during the past 3 days on an 11-point NRS at each study visit
- The primary effectiveness endpoint is the change in average pain intensity during the last 3 days (NRS-3) from the randomization visit (baseline) to final evaluation at the end of the continuation period in the per protocol set (defined below)
- Changes in neuropathic pain symptoms based on the painDETECT questionnaire and the Neuropathic Pain Symptom Inventory (NPSI) are evaluated as secondary endpoints
  - The painDETECT questionnaire[13] is completed at the enrollment visit, the randomization visit, at the end of titration (Visit 8), and at the final evaluation visit
    - The painDETECT questionnaire,[13] a patient-reported assessment validated for both screening and control, includes 7 questions addressing the frequency and quality of neuropathic pain symptoms (scored from 0-5; 0 = "never" to 5 = "very strongly"), 1 question addressing pain patterns over time, and 1 question evaluating radiating pain
  - The NPSI[14] is completed at the enrollment visit, 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 NPSI[14] is a validated measure that includes 10 items 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 mean daily doses of tapentadol PR and oxycodone/naloxone PR were evaluated at the end of titration

Statistical Analyses

- This study has an adaptive 3-stage group-sequential design (O'Brien and Fleming type design[15]), with 1 planned interim analysis after observation of one-third of the total planned study population, the results of which are presented here
- A 2-sample *t* test was used for the calculation of the sample size. The sample size computation for the primary effectiveness endpoint was based on a standard deviation (SD) of 2.5 for the change in pain intensity from baseline and a non-inferiority margin of 1.3; the sample size computation for the second endpoint was based on a SD of 1.0 for the change from baseline in the Patient Assessment of Constipation Symptoms (PAC-SYM) total score, an expected difference of 0.1 in the change from baseline in the PAC-SYM total score in favor of oxycodone/naloxone PR, and a non-inferiority margin of 0.7
  - For both endpoints, a sample size of 96 patients per group in the per protocol set (defined below) is 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 are available for the per protocol set, a total of 240 patients should receive study treatment in the overall study
  - Statistical methods for the second primary endpoint are explained in further detail in poster **<<XX>>** ***<<Poster number will be added upon receipt>>***
- For the final analysis of the primary effectiveness endpoint, tapentadol immediate release is considered to be non-inferior to oxycodone/naloxone PR if the upper limit of the 2-sided 97.5% repeated confidence interval (RCI) for the treatment difference (tapentadol PR minus oxycodone/naloxone PR) is less than the non-inferiority margin of 1.3
  - For this interim analysis, the test statistics of the normal inverse method were used to demonstrate non-inferiority (as described below)
- The safety set includes all randomized patients who took ≥1 dose of study drug
- The full analysis set includes all randomized patients who took ≥1 dose of study drug and had ≥1 post-baseline pain intensity assessment (NRS-3)

- The per protocol set is a subpopulation of the full analysis set that includes all patients who had no major protocol deviations that could impact the primary outcomes of the study
- The main analysis for the primary efficacy endpoint is adjusted for the group-sequential design and multiplicity, guaranteeing overall control of type I error rate (2.5% one-sided)
  - These results are based on the inverse normal method,[16] and those test statistics are shown in the current poster and compared to the appropriate critical value for the primary efficacy endpoint (3.935)
- All other analyses are exploratory, and all *P* values shown are descriptive *P* values
- For the painDETECT questionnaire, scores for the 9 individual questions are summed to yield a total painDETECT score (possible score, 0-38)
- For the NPSI, scores for the 10 individual items evaluating the properties of neuropathic pain are averaged and divided by 10 to yield 5 subscores (each with a possible score of 0-1): 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 are also summed and divided by 100 to yield an overall feeling score (possible score, 0-1)
- The changes from baseline to final evaluation in pain intensity (NRS-3; primary endpoint), the total painDETECT score, and the NPSI subscores and overall feeling score are evaluated using an analysis of covariance model including treatment and pooled center as factors and score at baseline as a covariate
  - The last observation carried forward (LOCF) is used for imputing missing scores
  - The patients who entered the pickup arm were treated as discontinuations using the LOCF. The pickup arm was not analyzed during this interim analysis

RESULTS

Patients and Dosing

- For this interim analysis, 77 patients (tapentadol PR, n = 38; oxycodone/naloxone PR, n = 39) were included in the safety set and in the full analysis set, and 66 patients (tapentadol PR, n = 31; oxycodone/naloxone PR, n = 35) were included in the per protocol set
- Demographic characteristics were comparable between treatment groups in the safety set (**Table 2**)

Table 2. Demographics and Study Population (Safety Set)

Characteristic	Tapentadol PR (n = 38)	Oxycodone/naloxone PR (n = 39)
Mean (SD) age, years	55.8 (12.33)	58.7 (11.76)
Gender, n (%)		
Female	24 (63.2)	22 (56.4)
Male	14 (36.8)	17 (43.6)
Mean (SD) BMI, kg/m^2	29.6 (5.85)	28.7 (5.53)
Race, n (%)		
White	38 (100.0)	39 (100.0)

PR, prolonged release; SD, standard deviation; BMI, body mass index.

- A total of 76.3% (29/38) patients in the tapentadol PR group, and 76.9% (30/39) of patients in the oxycodone/naloxone PR group had a diagnosis of lumbar radiculopathy at baseline
- During the titration period, 10.5% (4/38) of patients in the tapentadol PR group and 46.2% (18/39) of patients in the oxycodone/naloxone PR group discontinued the study, while during the overall treatment period, 21.1% (8/38) of patients in the tapentadol PR group and 59.0% (23/39) of patients in the oxycodone/naloxone PR group discontinued the study
  - The most common reasons for treatment discontinuation during the overall study were adverse events and a lack of efficacy
  - In the tapentadol PR and oxycodone/naloxone PR groups, respectively, adverse events led to discontinuation in 5.3% (2/38) and 30.8% (12/39) of patients during the titration period and in 10.5% (4/38) and 33.3% (13/39) of patients during the overall treatment period, while a lack of efficacy led to discontinuation in 0% and 7.7% (3/39) of patients during the titration period and in 0% and 12.8% (5/39) of patients during the overall treatment period
- In the tapentadol PR and oxycodone/naloxone PR groups, respectively, 79% (30/38) and 41% (16/39) of patients in the safety set completed study treatment
  - Overall, 92% more patients stayed on tapentadol PR treatment compared with oxycodone/naloxone PR treatment
- At the end of titration, the mean SD daily doses were **<<X.XX>>** mg/day in the tapentadol PR group and **<<X.XX>>** mg/day in the oxycodone/naloxone PR group

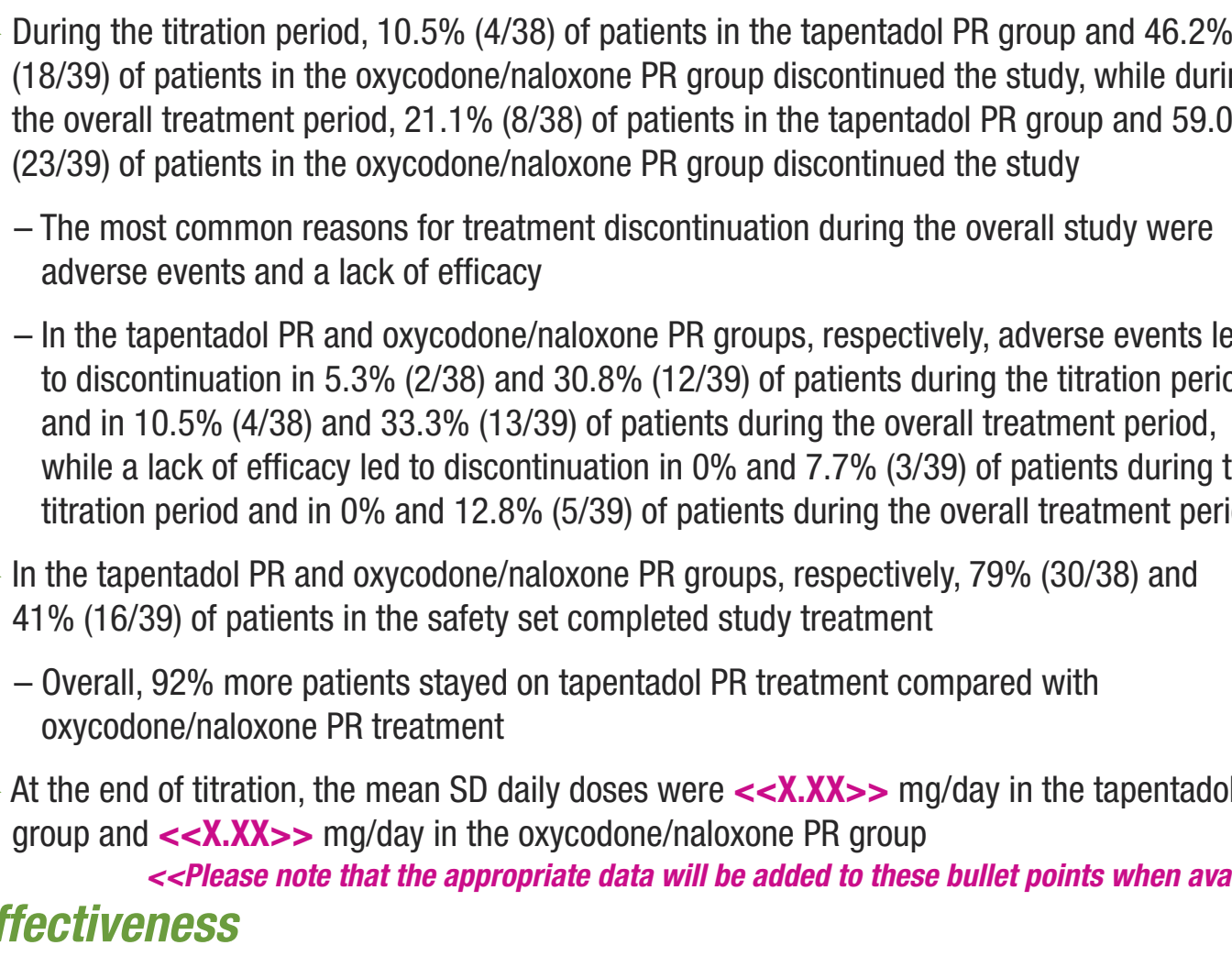
<<Please note that the appropriate data will be added to these bullet points when available>>

Effectiveness

- For the primary effectiveness endpoint, significant and clinically important reductions[17] in pain intensity from baseline to final evaluation (LOCF) were observed for both tapentadol PR and oxycodone/naloxone PR in the per protocol set (both $P<0.001$ for the change from baseline)
  - From baseline to final evaluation, pain intensity decreased by –4.3 (55.8%) in the tapentadol PR group and by –2.8 (37.3%) in the oxycodone/naloxone PR group (**Figure 1**)
  - The test statistic of the inverse normal method (4.348) exceeded the appropriate critical value (3.935) at stage 1 of the 3-stage group sequential design, showing that the reduction in pain intensity from baseline to final evaluation observed with tapentadol PR was non-inferior to that observed with oxycodone/naloxone PR
- In addition, the reduction in pain intensity from baseline to final evaluation was significantly greater with tapentadol PR than with oxycodone/naloxone PR (least-squares mean difference [97.5% confidence interval (CI)], –1.5 [–2.9,–0.2]; $P = 0.0062$; exploratory analysis; **Figure 1**)
  - At final evaluation, tapentadol PR showed 53.6% more pain reduction (based on mean pain intensity) compared to oxycodone/naloxone PR (**Figure 1**)

Neuropathic Pain-related Symptoms

- The total painDETECT score decreased significantly from baseline to final evaluation (LOCF) in both treatment groups in the full analysis set (both $P<0.001$ for the change from baseline; **Table 1** and **Figure 3**)
- From baseline to final evaluation, the total painDETECT score decreased by –10.5 (46.4%) in the tapentadol PR group and by –6.0 (27.8%) in the oxycodone/naloxone PR group
- The decrease in the total painDETECT score from baseline to final evaluation was significantly greater in the tapentadol PR group than in the oxycodone/naloxone PR group (least-squares mean difference [95% CI], –4.5 [–7.9, –1.1]; $P = 0.010$)
  - At final evaluation, the painDETECT score was reduced by 75% more in the tapentadol PR than in the oxycodone/naloxone PR

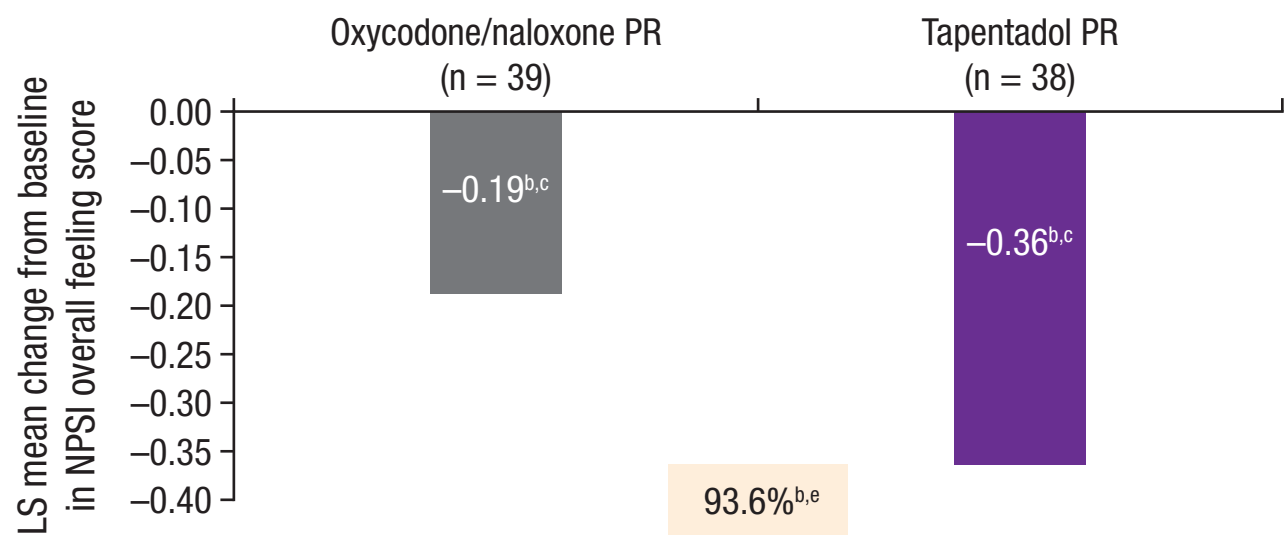


LS, least-squares; LOCF, last observation carried forward; PR, prolonged release.
[a]Descriptive analyses.
[b]Percent difference from baseline.
[c]LS means and *P* values are obtained from an analysis of covariance model that includes treatment and pooled centers as factors and score at randomization (baseline) as a covariate.
[d]$P<0.001$ for the change from baseline.
[e]$P = 0.01$ (superiority; tapentadol PR vs oxycodone/naloxone PR).
[f]Percent difference between tapentadol PR and oxycodone/naloxone PR, using oxycodone/naloxone PR as the base (denominator).

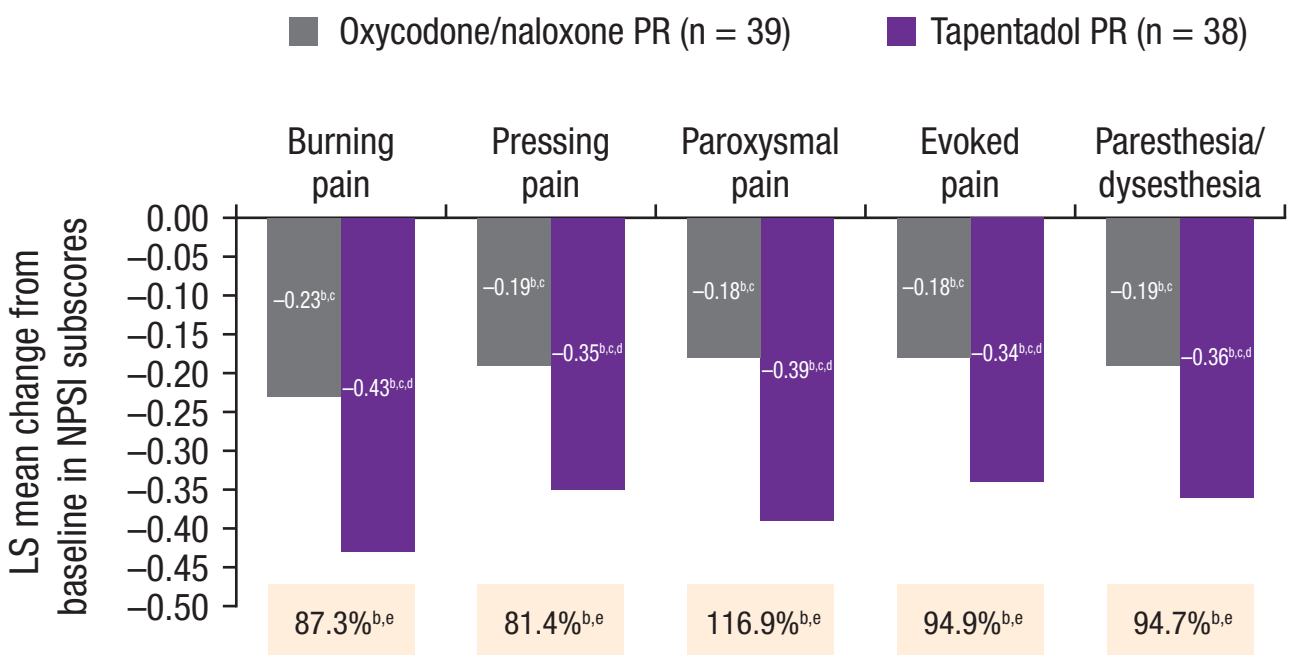
Figure 3. Mean total painDETECT score at baseline and Week 12 and change in the total painDETECT score from baseline to final evaluation (LS mean; LOCF; full analysis set).[a]

- The NPSI overall feeling score decreased significantly from baseline to final evaluation in the tapentadol PR group and the oxycodone/naloxone PR group (both $P<0.001$; **Figure 4A**)
  - The NPSI overall feeling score decreased by 93.6% more in the tapentadol PR group than in the oxycodone/naloxone PR group (**Figure 4A**)
- A significant decrease from baseline to final evaluation (LOCF) was also observed in the NPSI subscores in both treatment groups in the full analysis set (all $P<0.001$ for the change from baseline; **Table 1**, **Figure 4B**, and **Figure 5**)
  - The improvements in all NPSI subscores were significantly greater in the tapentadol PR group than in the oxycodone/naloxone PR group (all $P \leq 0.003$; **Figure 4A**)
    - NPSI subscores decreased from baseline to final evaluation by 81.4% to 116.9% more with tapentadol PR than with oxycodone/naloxone PR (**Figure 4B**)

A. NPSI overall feeling score



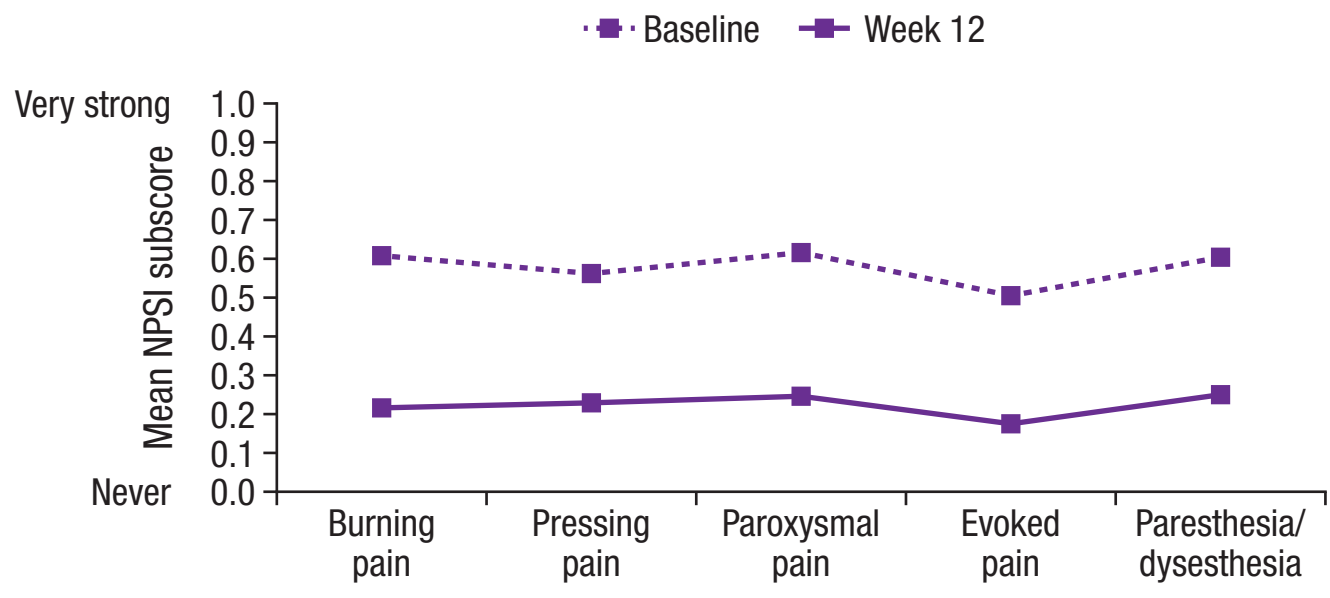
B. NPSI subscale scores



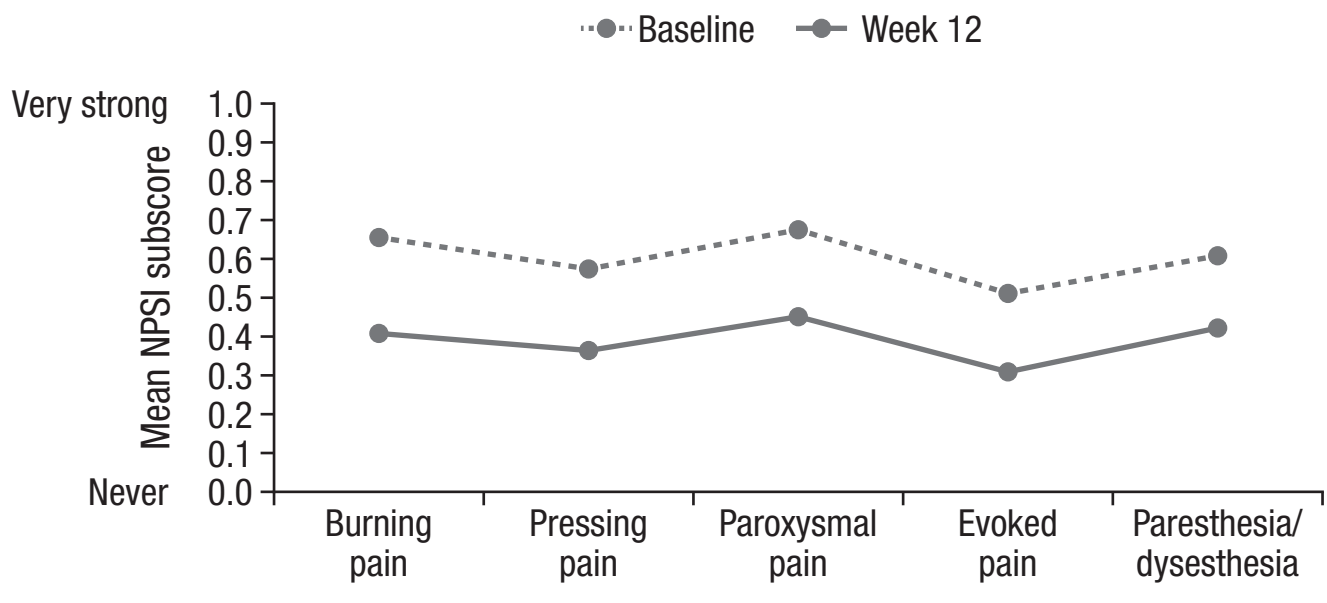
NPSI, Neuropathic Pain Symptom Inventory; LS, least-squares; LOCF, last observation carried forward; PR, prolonged release.
[a]Descriptive analyses.
[b]LS means and *P* values are obtained from an analysis of covariance model that includes treatment and pooled centers as factors and score at randomization (baseline) as a covariate.
[c]$P<0.001$ for the change from baseline.
[d]$P \leq 0.003$ (superiority; tapentadol PR vs oxycodone/naloxone PR).
[e]Percent difference between tapentadol PR and oxycodone/naloxone PR, using oxycodone/naloxone PR as the base (denominator).

Figure 4. Changes from baseline to final evaluation in the NPSI A) overall feeling score and B) subscale scores (LS mean; LOCF; full analysis set).[a]

A. Tapentadol PR



B. Oxycodone/naloxone PR



NPSI, Neuropathic Pain Symptom Inventory; LOCF, last observation carried forward; PR, prolonged release.

Figure 5. Mean NPSI subscores at baseline and Week 12 (LOCF; full analysis set).

CONCLUSIONS

- **In this interim analysis, both tapentadol PR and oxycodone/naloxone PR provided significant reductions in pain intensity from baseline to final evaluation**
  - **The effectiveness of tapentadol PR was non-inferior to oxycodone/naloxone PR**
- **Tapentadol PR was shown to have superior effectiveness to oxycodone/naloxone PR (descriptive analysis)**
  - **Tapentadol PR was associated with 53.6% more pain reduction than oxycodone/naloxone PR**
- **Both tapentadol PR and oxycodone/naloxone PR were associated with significant improvements in neuropathic pain-related symptoms from baseline to final evaluation, based on changes in the painDETECT and NPSI questionnaires**
  - **Tapentadol PR was associated with significantly greater improvements from baseline to final evaluation in all measures of neuropathic pain-related symptoms than oxycodone/naloxone PR (descriptive analyses)**
- **This interim analysis is subject to certain limitations**
  - **The current interim analysis is based on a relatively small sample size; the final outcome may differ for the full study population**
  - **All of the *P* values presented here are descriptive and not adjusted for type 1 error inflation, which may lead to an increased false positive rate**
- **Overall, results indicate that tapentadol PR is effective in managing severe chronic pain and is superior to oxycodone/naloxone PR in providing strong pain relief**
  - **These results also indicated that tapentadol PR is associated with greater improvements in neuropathic pain-related symptoms than oxycodone/naloxone PR; these improvements were even greater than the reduction in spontaneous pain measured using the NRS-3**

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