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

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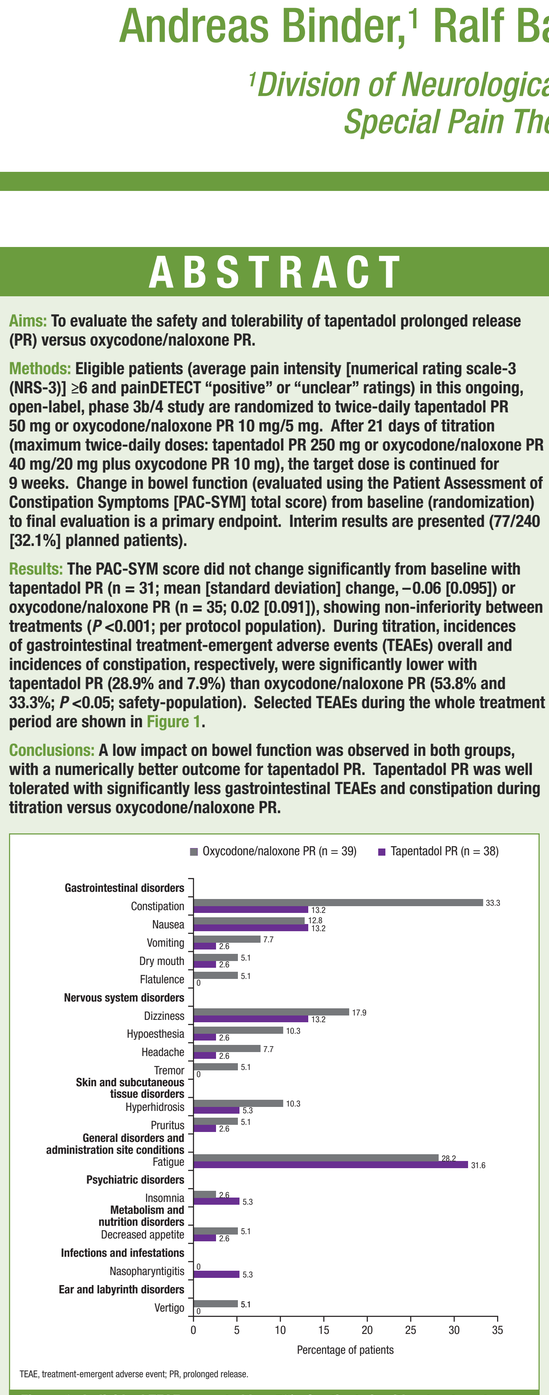
ABSTRACT

Aims: **To evaluate the safety and tolerability of tapentadol prolonged release (PR) versus oxycodone/naloxone PR.**

Methods: **Eligible patients (average pain intensity [numerical rating scale-3 (NRS-3)] ≥6 and painDETECT "positive" or "unclear" ratings) in this ongoing, open-label, phase 3b/4 study 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), the target dose is continued for 9 weeks. Change in bowel function (evaluated using the Patient Assessment of Constipation Symptoms [PAC-SYM] total score) from baseline (randomization) to final evaluation is a primary endpoint. Interim results are presented (77/240 [32.1%] planned patients).**

Results: **The PAC-SYM score did not change significantly from baseline with tapentadol PR (n = 31; mean [standard deviation] change, −0.06 [0.095]) or oxycodone/naloxone PR (n = 35; 0.02 [0.091]), showing non-inferiority between treatments (*P* <0.001; per protocol population). During titration, incidences of gastrointestinal treatment-emergent adverse events (TEAEs) overall and incidences of constipation, respectively, were significantly lower with tapentadol PR (28.9% and 7.9%) than oxycodone/naloxone PR (53.8% and 33.3%; *P* <0.05; safety-population). Selected TEAEs during the whole treatment period are shown in Figure 1.**

Conclusions: **A low impact on bowel function was observed in both groups, with a numerically better outcome for tapentadol PR. Tapentadol PR was well tolerated with significantly less gastrointestinal TEAEs and constipation during titration versus oxycodone/naloxone PR.**



TEAE, treatment-emergent adverse event; PR, prolonged release.

Figure 1. Individual TEAEs reported by ≥5% of patients in either treatment group during the whole treatment period (safety population, interim results).

INTRODUCTION

- Opioids may be used for the management of chronic pain, but may not be effective for pain with a neuropathic component[1,2] and may be associated with side effects, particularly gastrointestinal side effects, which lead patients to reduce or skip doses of their opioid analgesics or discontinue treatment[3-5] or may lead physicians to under-prescribe opioids for chronic pain[6]
  - Opioid-induced constipation can be particularly problematic for chronic pain patients because it may be refractory to standard treatments and tolerance to this side effect often does not develop[4,7]
- Tapentadol is a centrally acting analgesic with μ-opioid receptor agonist and noradrenaline reuptake inhibitor activities[8,9]
  - Tapentadol prolonged release (PR) has been shown to be effective for the management of severe, chronic low back pain with a neuropathic pain component in recent phase 3b studies[10,11]
  - Tapentadol PR has also been shown to be effective for the management of other types of moderate to severe, chronic pain, including osteoarthritis knee pain,[12,13] low back pain,[13,14] pain related to diabetic peripheral neuropathy,[15] and cancer pain[16] with improved tolerability (particularly gastrointestinal tolerability) compared with oxycodone PR (for osteoarthritis and low back pain)[12-14] and morphine controlled release (for cancer pain)[16]
- Fixed-dose combinations of oxycodone/naloxone PR have also demonstrated efficacy for the management of moderate to severe, chronic low back pain,[17] with better gastrointestinal tolerability compared with oxycodone PR alone[17,18]
  - 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[18]

OBJECTIVES

- To evaluate the safety and tolerability 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
- Effectiveness results, including results of the primary effectiveness endpoint, 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>>***

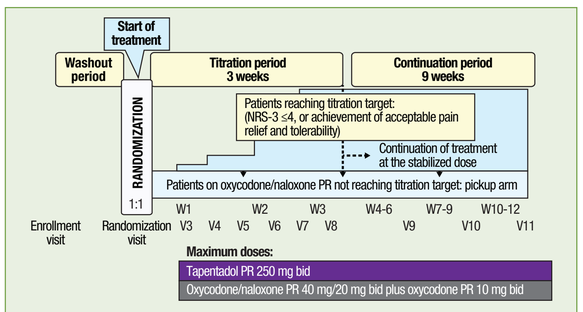
METHODS

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[19] (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 1 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

- A second primary endpoint of the study is the change in the Patient Assessment of Constipation Symptoms (PAC-SYM) total score from the randomization visit (baseline) to final evaluation at the end of the continuation period
  - The PAC-SYM is evaluated at the randomization visit (baseline) and at final evaluation
  - The PAC-SYM[20,21] is a validated, 12-item, patient self-administered questionnaire that measures the severity of constipation symptoms; each item is scored using a 5-point scale (0 = "absent" to 4 = "very severe")
  - The 12 items of the PAC-SYM are summarized in 3 subscale scores: stool symptoms (5 items), abdominal symptoms (4 items), and rectal symptoms (3 items)
  - The PAC-SYM total score is the sum of the scores for all non-missing items divided by the number of non-missing items if ≥6 items are non-missing
- Treatment-emergent adverse events (TEAEs) and discontinuations are monitored and recorded throughout the study
  - The mean daily doses of tapentadol PR and oxycodone/naloxone PR were evaluated at the end of titration

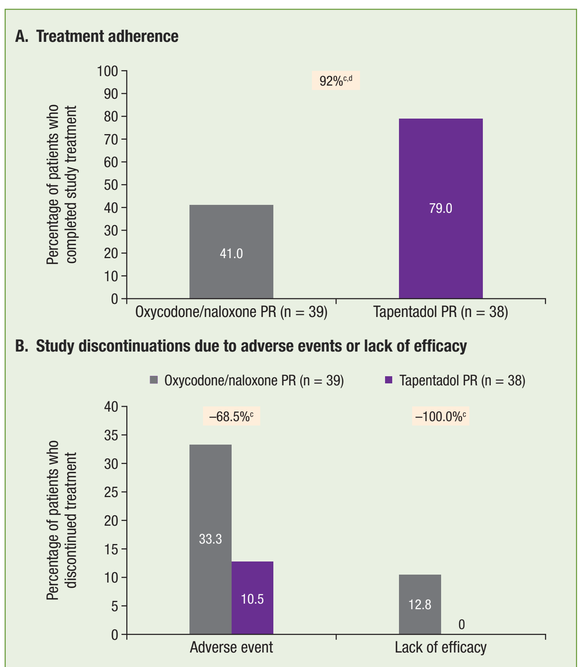
Statistical Analyses

- This study has an adaptive 3-stage group-sequential design (O'Brien and Fleming type design[22]), 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, and the sample size computation for the second endpoint was based on a SD of 1.0 for the change from baseline in the 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 primary effectiveness endpoint are explained in further detail in poster <<XX>>***<<Poster number will be added upon receipt>>***
- 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)
- For the main analysis of the second primary endpoint for the study (the change from baseline to final evaluation in the mean PAC-SYM score), tapentadol PR is considered to be non-inferior to oxycodone/naloxone PR if the upper limit of the 2-sided 97.5% repeated confidence interval (CI) for the treatment difference (tapentadol PR minus oxycodone/naloxone PR) is less than the non-inferiority margin of 0.7
  - For this interim analysis, the test statistics of the normal inverse method were used to demonstrate non-inferiority (as described below)
- These results are based on the inverse normal method[23] and those test statistics are shown in the current poster and compared to the appropriate critical value for the second primary endpoint (3.935)
- All other analyses are exploratory, and all *P* values shown are descriptive *P* values
- The changes from baseline to final evaluation in pain intensity (NRS-3; primary efficacy endpoint) and in the mean PAC-SYM score (primary endpoint) 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

- For this interim analysis, 77 patients were included in the safety set and the full analysis set
- 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, 63.2% [24/38]; oxycodone/naloxone PR, 56.4% [22/39])
  - The mean (SD) age was 55.8 (12.33) years in the tapentadol PR group and 58.7 (11.76) years in the oxycodone/naloxone PR group
- The percentage of patients who completed study treatment in each treatment group are summarized in **Figure 3A**
  - Overall, 92% more patients remained on tapentadol PR treatment compared with oxycodone/naloxone PR treatment
- Study discontinuations due to adverse events or lack of efficacy in the safety set are summarized in **Figure 3B**
  - There were no discontinuations due to a lack of efficacy in the tapentadol PR group
- 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

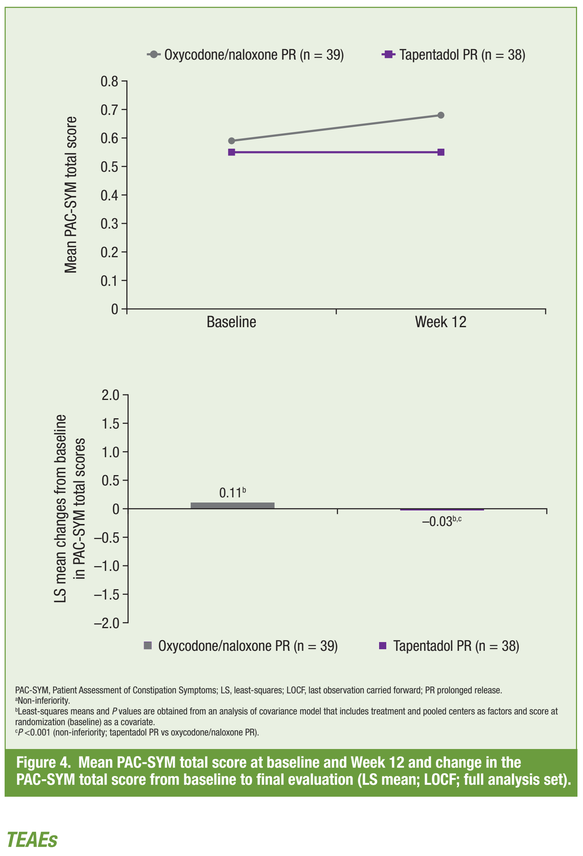


PR, prolonged release; TEAE, treatment-emergent adverse event.
[a]Includes patients who switched to the pickup arm due to TEAEs.
[b]Additional reasons for study discontinuation included withdrawal by the patient (tapentadol PR, 2.6% [1/38]; oxycodone/naloxone PR, 7.7% [3/39]); technical reasons (tapentadol PR, 0%; oxycodone/naloxone PR, 2.6% [1/39]); protocol deviations (tapentadol PR 2.6% [2/38]; oxycodone/naloxone PR, 0%); and other reasons (tapentadol PR, 5.3% [2/38]; oxycodone/naloxone PR, 0%).
[c]Percent difference between tapentadol PR and oxycodone/naloxone PR using oxycodone/naloxone PR as the base (denominator).
[d]Ninety-two percent more patients stayed on tapentadol PR compared with oxycodone/naloxone PR.

Figure 3. A) Incidence of treatment adherence and B) treatment discontinuations due to adverse events[a] or lack of efficacy (safety set).[b]

PAC-SYM

- No statistically significant changes from baseline were observed in the mean PAC-SYM score in either treatment group of the full analysis set (LOCF; **Figure 4**)
  - The least-squares mean difference (97.5% CI) for the PAC-SYM total score was −0.14 (−0.44, 0.16); $P < 0.001$)
  - The test statistic of the inverse normal method (5.601) exceeded the appropriate critical value (3.935) at stage 1 of the 3-stage group-sequential design, indicating that the change in constipation symptoms observed with tapentadol PR was non-inferior to that observed with oxycodone/naloxone PR

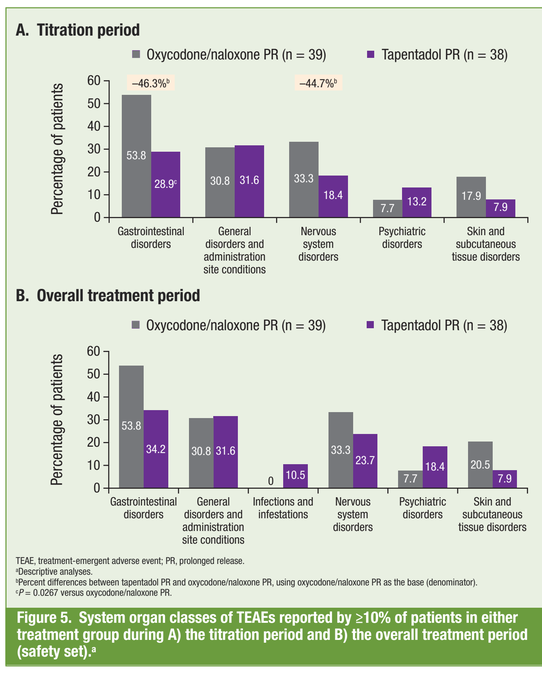


PAC-SYM, Patient Assessment of Constipation Symptoms; LS, least-squares; LOCF, last observation carried forward; PR prolonged release.
[a]Non-inferiority.
[b]Least-squares means and *P* values are obtained from an analysis of covariance model that includes treatment and pooled centers as factors and score at randomization (baseline) as a covariate.
[c]$P < 0.001$ (non-inferiority; tapentadol PR vs oxycodone/naloxone PR).

Figure 4. Mean PAC-SYM total score at baseline and Week 12 and change in the PAC-SYM total score from baseline to final evaluation (LS mean; LOCF; full analysis set).

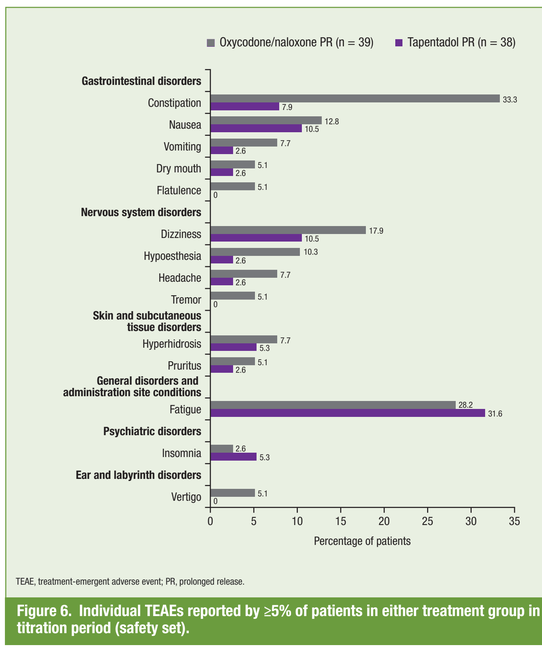
TEAEs

- During the titration period, the overall incidence of TEAEs was 63.2% (24/38) in the tapentadol PR group and 71.8% (28/39) in the oxycodone/naloxone PR group of the safety set
  - System organ classes of TEAEs reported by ≥10% of patients in either treatment group during the titration period are summarized in **Figure 5A**
  - Individual TEAEs reported by ≥5% of patients in either treatment group during the titration period are summarized in **Figure 6A**
    - The incidence of gastrointestinal TEAEs overall and the incidence of constipation were significantly lower in the tapentadol PR group than in the oxycodone/naloxone PR group during titration (both $P \leq 0.05$; **Figure 5A** and **Figure 7**)
    - Patients in the tapentadol PR group presented a 46.3% lower incidence of gastrointestinal TEAEs overall and a 76.3% lower incidence of constipation than those in the oxycodone/naloxone PR group



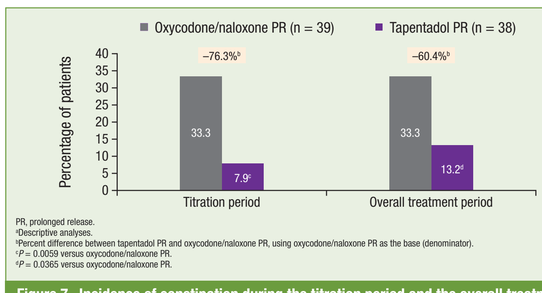
TEAE, treatment-emergent adverse event; PR, prolonged release.
[a]Descriptive analyses.
[b]Percent differences between tapentadol PR and oxycodone/naloxone PR, using oxycodone/naloxone PR as the base (denominator).
[c]$P = 0.0267$ versus oxycodone/naloxone PR.

Figure 5. System organ classes of TEAEs reported by ≥10% of patients in either treatment group during A) the titration period and B) the overall treatment period (safety set).[a]



TEAE, treatment-emergent adverse event; PR, prolonged release.

Figure 6. Individual TEAEs reported by ≥5% of patients in either treatment group in the titration period (safety set).



PR, prolonged release.
[a]Descriptive analyses.
[b]Percent difference between tapentadol PR and oxycodone/naloxone PR, using oxycodone/naloxone PR as the base (denominator).
[c]$P = 0.0059$ versus oxycodone/naloxone PR.
[d]$P = 0.0365$ versus oxycodone/naloxone PR.

Figure 7. Incidence of constipation during the titration period and the overall treatment period (safety set).[a]

- During the entire study period, the overall incidence of TEAEs was 73.7% (28/38) in the tapentadol PR group and 82.1% (32/39) in the oxycodone/naloxone PR group of the safety set
  - System organ classes of TEAEs reported by ≥10% of patients in either treatment group during the overall treatment period are summarized in **Figure 5B**, and individual TEAEs reported by ≥5% of patients in either treatment group during the overall treatment period are summarized in **Figure 6B**
    - The incidence of constipation was 60% lower in the tapentadol PR group than in the oxycodone/naloxone PR group during the overall study (**Figure 6B** and **Figure 7**)

CONCLUSIONS

- **For the second primary endpoint in this interim analysis, a low impact on bowel function (based on the PAC-SYM) was observed in both treatment groups, with a numerically better outcome for tapentadol PR**
- **Both tapentadol PR and oxycodone/naloxone PR were well tolerated**
  - **Tapentadol PR was associated with 60% less constipation than oxycodone/naloxone PR during the overall treatment period**
  - **In addition, tapentadol PR was associated with a lower incidence of both gastrointestinal TEAEs overall and constipation during the titration period compared with oxycodone/naloxone PR**
- **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**
- **Taken together, results of the current interim analysis indicate that tapentadol PR presents a favorable tolerability profile, with improved gastrointestinal tolerability compared with oxycodone/naloxone PR**

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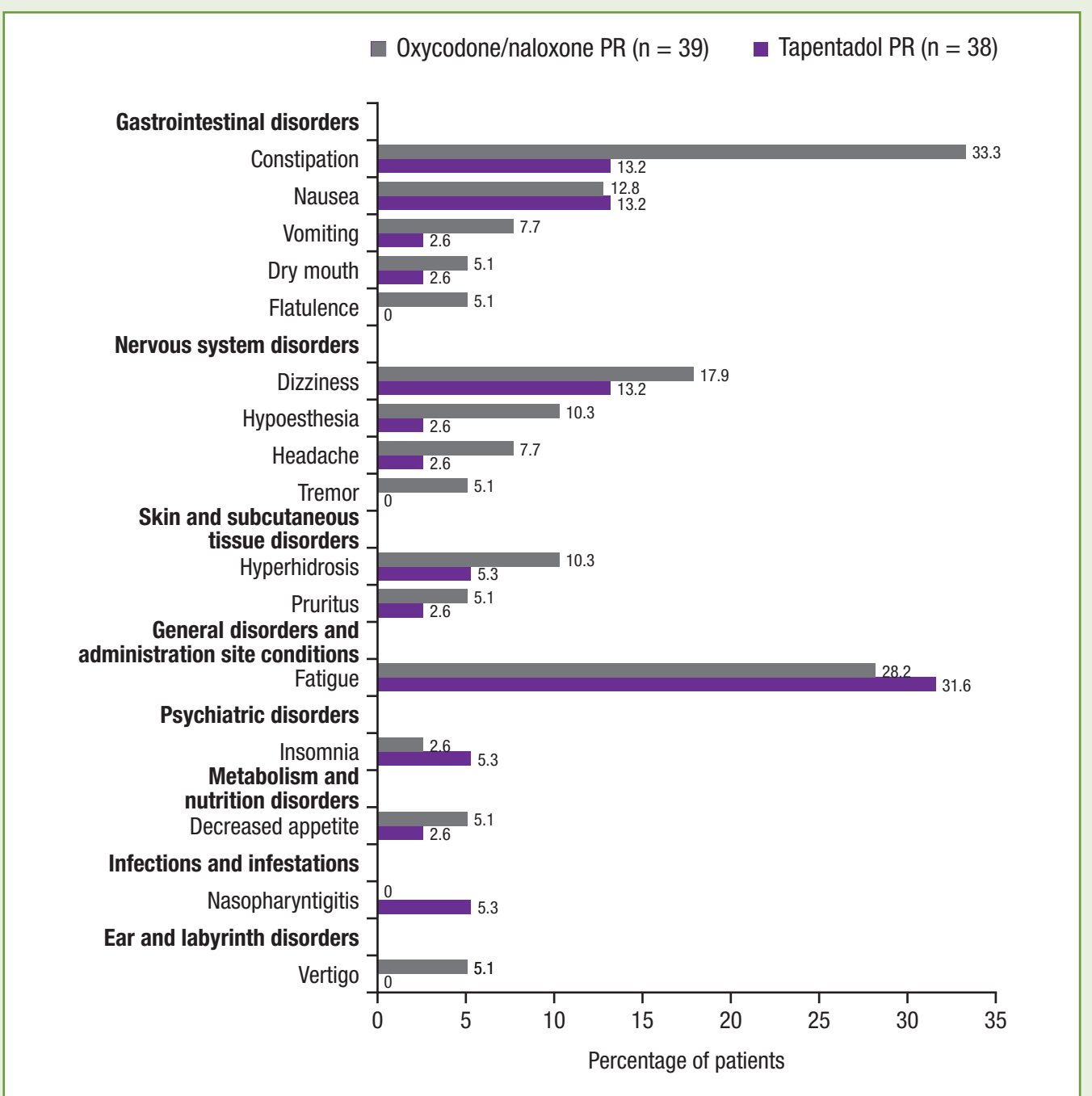
Methods: Eligible patients (average pain intensity [numerical rating scale-3 (NRS-3)] ≥6 and painDETECT "positive" or "unclear" ratings) in this ongoing, open-label, phase 3b/4 study are randomized to twice-daily tapentadol PR 50 mg or oxycodone/naloxone PR 10 mg/5 mg. After 21 days of titration (maximum twice-daily doses: tapentadol PR 250 mg or oxycodone/naloxone PR 40 mg/20 mg plus oxycodone PR 10 mg), the target dose is continued for 9 weeks. Change in bowel function (evaluated using the Patient Assessment of Constipation Symptoms [PAC-SYM] total score) from baseline (randomization) to final evaluation is a primary endpoint. Interim results are presented (77/240 [32.1%] planned patients).

Results: The PAC-SYM score did not change significantly from baseline with tapentadol PR (n = 31; mean [standard deviation] change, −0.06 [0.095]) or oxycodone/naloxone PR (n = 35; 0.02 [0.091]), showing non-inferiority between treatments (*P* <0.001; per protocol population). During titration, incidences of gastrointestinal treatment-emergent adverse events (TEAEs) overall and incidences of constipation, respectively, were significantly lower with tapentadol PR (28.9% and 7.9%) than oxycodone/naloxone PR (53.8% and 33.3%; *P* <0.05; safety-population). Selected TEAEs during the whole treatment period are shown in Figure 1.

Conclusions: A low impact on bowel function was observed in both groups, with a numerically better outcome for tapentadol PR. Tapentadol PR was well tolerated with significantly less gastrointestinal TEAEs and constipation during titration versus oxycodone/naloxone PR.



TEAE, treatment-emergent adverse event; PR, prolonged release.

Figure 1. Individual TEAEs reported by ≥5% of patients in either treatment group during the whole treatment period (safety population, interim results).

INTRODUCTION

- Opioids may be used for the management of chronic pain, but may not be effective for pain with a neuropathic component[1,2] and may be associated with side effects, particularly gastrointestinal side effects, which lead patients to reduce or skip doses of their opioid analgesics or discontinue treatment[3-5] or may lead physicians to under-prescribe opioids for chronic pain[6]
  - Opioid-induced constipation can be particularly problematic for chronic pain patients because it may be refractory to standard treatments and tolerance to this side effect often does not develop[4,7]
- Tapentadol is a centrally acting analgesic with μ-opioid receptor agonist and noradrenaline reuptake inhibitor activities[8,9]
  - Tapentadol prolonged release (PR) has been shown to be effective for the management of severe, chronic low back pain with a neuropathic pain component in recent phase 3b studies[10,11]
  - Tapentadol PR has also been shown to be effective for the management of other types of moderate to severe, chronic pain, including osteoarthritis knee pain,[12,13] low back pain,[13,14] pain related to diabetic peripheral neuropathy,[15] and cancer pain[16] with improved tolerability (particularly gastrointestinal tolerability) compared with oxycodone PR (for osteoarthritis and low back pain)[12-14] and morphine controlled release (for cancer pain)[16]
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  - 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[18]

OBJECTIVES

- To evaluate the safety and tolerability 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
- Effectiveness results, including results of the primary effectiveness endpoint, 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

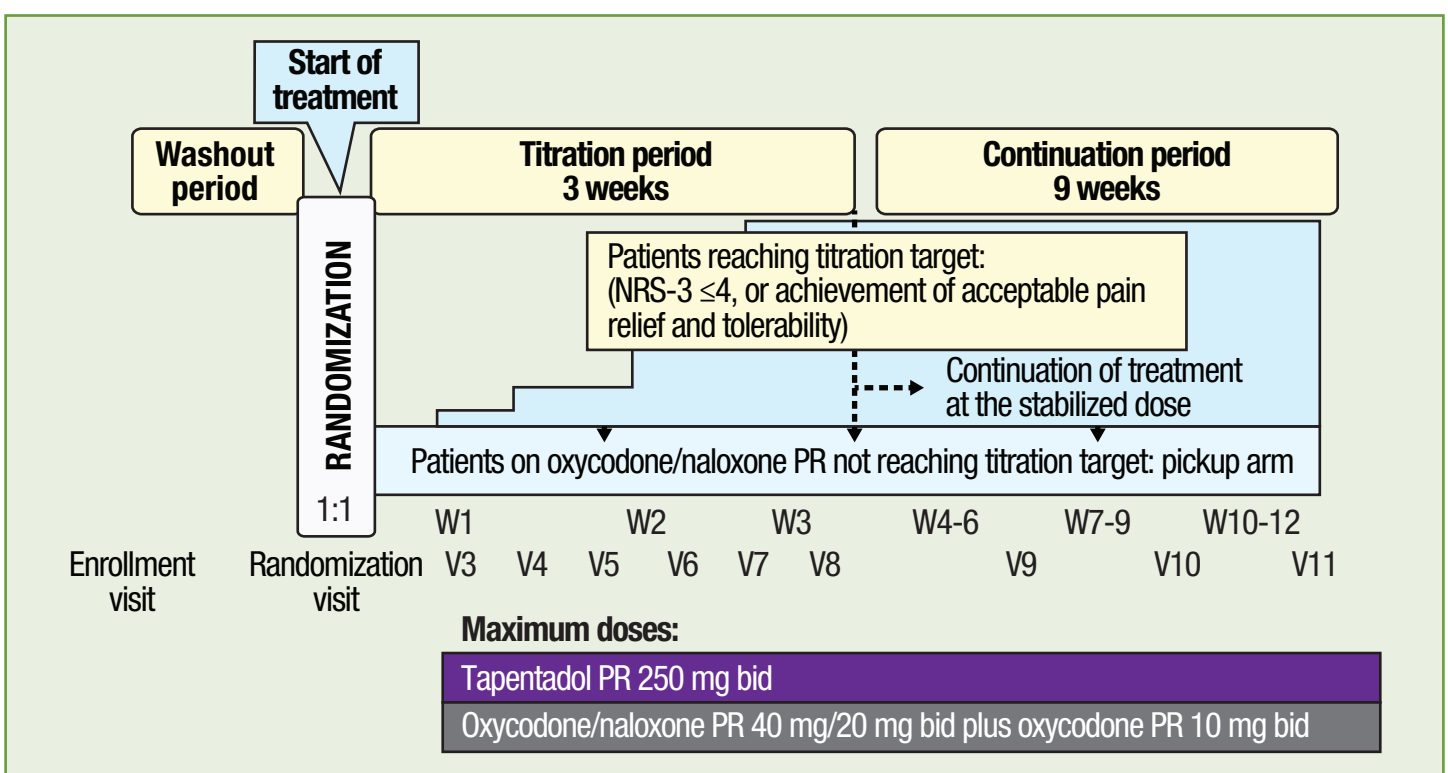
Patients

- 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[19] (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 1 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

- A second primary endpoint of the study is the change in the Patient Assessment of Constipation Symptoms (PAC-SYM) total score from the randomization visit (baseline) to final evaluation at the end of the continuation period
  - The PAC-SYM is evaluated at the randomization visit (baseline) and at final evaluation
  - The PAC-SYM[20,21] is a validated, 12-item, patient self-administered questionnaire that measures the severity of constipation symptoms; each item is scored using a 5-point scale (0 = "absent" to 4 = "very severe")
  - The 12 items of the PAC-SYM are summarized in 3 subscale scores: stool symptoms (5 items), abdominal symptoms (4 items), and rectal symptoms (3 items)
  - The PAC-SYM total score is the sum of the scores for all non-missing items divided by the number of non-missing items if ≥6 items are non-missing
- Treatment-emergent adverse events (TEAEs) and discontinuations are monitored and recorded throughout the study
  - The mean daily doses of tapentadol PR and oxycodone/naloxone PR were evaluated at the end of titration

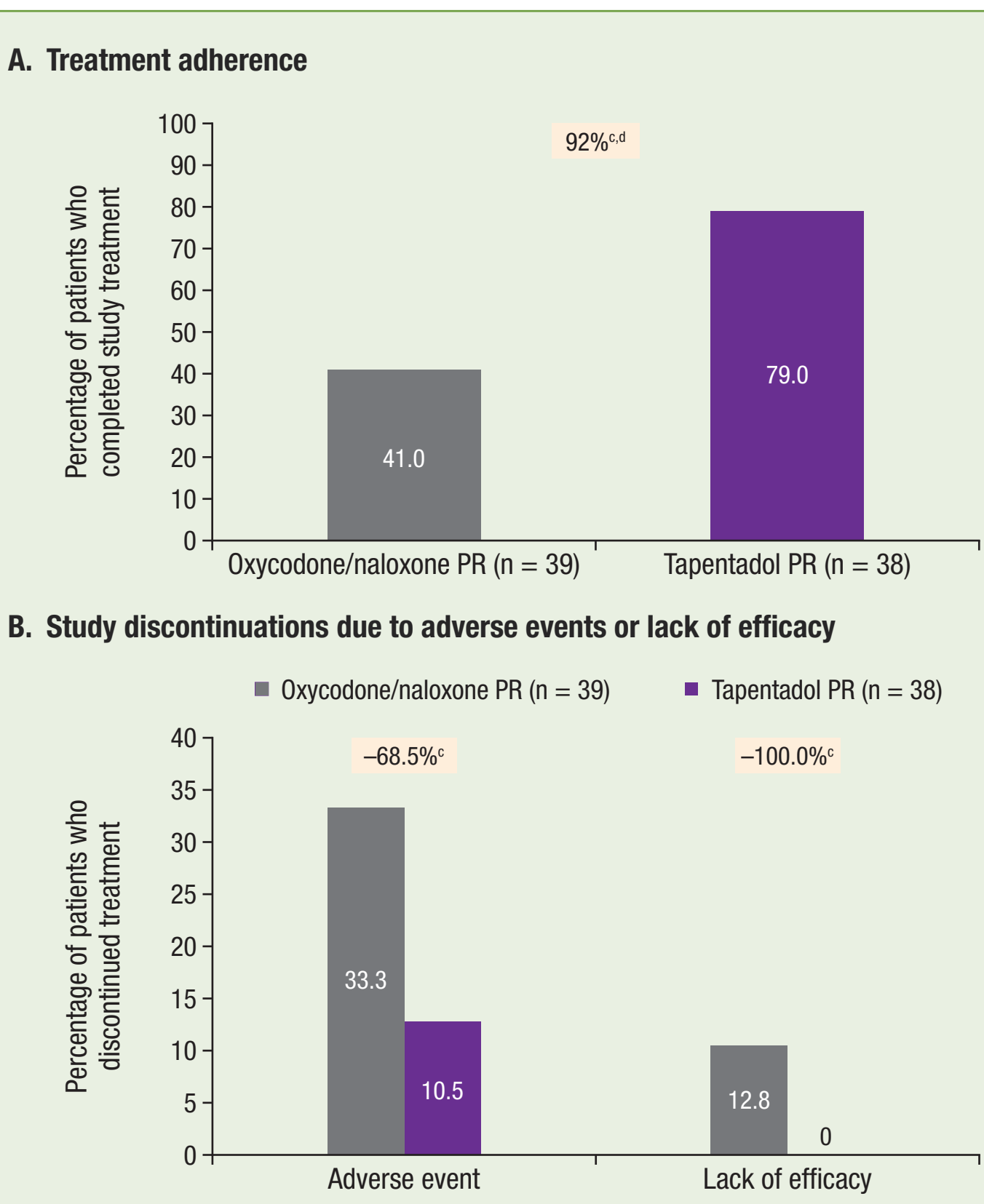
Statistical Analyses

- This study has an adaptive 3-stage group-sequential design (O'Brien and Fleming type design[22]), 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, and the sample size computation for the second endpoint was based on a SD of 1.0 for the change from baseline in the 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 primary effectiveness endpoint are explained in further detail in poster <<XX>>***<<Poster number will be added upon receipt>>***
- 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)
- For the main analysis of the second primary endpoint for the study (the change from baseline to final evaluation in the mean PAC-SYM score), tapentadol PR is considered to be non-inferior to oxycodone/naloxone PR if the upper limit of the 2-sided 97.5% repeated confidence interval (CI) for the treatment difference (tapentadol PR minus oxycodone/naloxone PR) is less than the non-inferiority margin of 0.7
  - For this interim analysis, the test statistics of the normal inverse method were used to demonstrate non-inferiority (as described below)
- These results are based on the inverse normal method[23] and those test statistics are shown in the current poster and compared to the appropriate critical value for the second primary endpoint (3.935)
- All other analyses are exploratory, and all *P* values shown are descriptive *P* values
- The changes from baseline to final evaluation in pain intensity (NRS-3; primary efficacy endpoint) and in the mean PAC-SYM score (primary endpoint) 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

- For this interim analysis, 77 patients were included in the safety set and the full analysis set
- 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, 63.2% [24/38]; oxycodone/naloxone PR, 56.4% [22/39])
  - The mean (SD) age was 55.8 (12.33) years in the tapentadol PR group and 58.7 (11.76) years in the oxycodone/naloxone PR group
- The percentage of patients who completed study treatment in each treatment group are summarized in **Figure 3A**
  - Overall, 92% more patients remained on tapentadol PR treatment compared with oxycodone/naloxone PR treatment
- Study discontinuations due to adverse events or lack of efficacy in the safety set are summarized in **Figure 3B**
  - There were no discontinuations due to a lack of efficacy in the tapentadol PR group
- 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

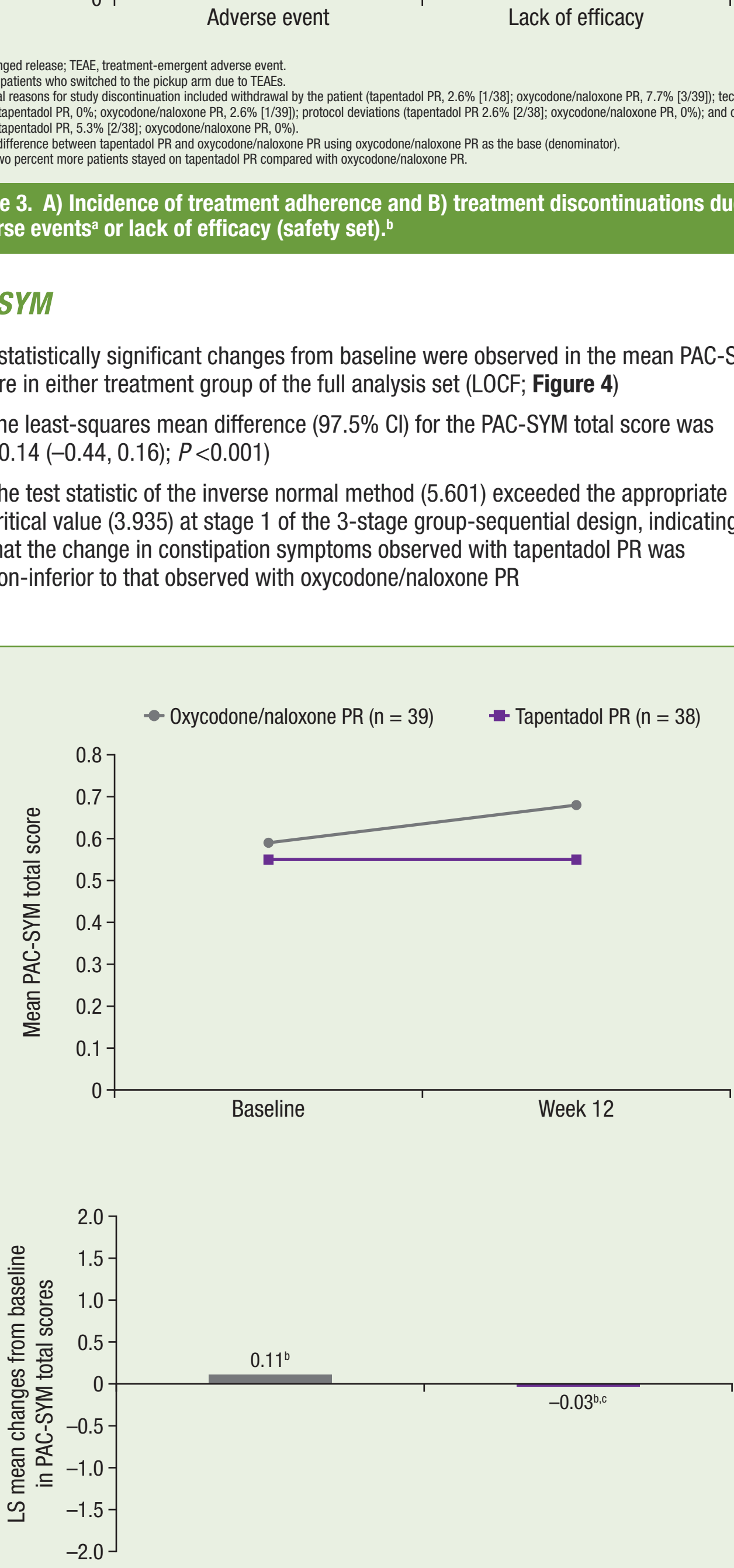


PR, prolonged release; TEAE, treatment-emergent adverse event.
[a]Includes patients who switched to the pickup arm due to TEAEs.
[b]Additional reasons for study discontinuation included withdrawal by the patient (tapentadol PR, 2.6% [1/38]; oxycodone/naloxone PR, 7.7% [3/39]); technical reasons (tapentadol PR, 0%; oxycodone/naloxone PR, 2.6% [1/39]); protocol deviations (tapentadol PR 2.6% [2/38]; oxycodone/naloxone PR, 0%); and other reasons (tapentadol PR, 5.3% [2/38]; oxycodone/naloxone PR, 0%).
[c]Percent difference between tapentadol PR and oxycodone/naloxone PR using oxycodone/naloxone PR as the base (denominator).
[d]Ninety-two percent more patients stayed on tapentadol PR compared with oxycodone/naloxone PR.

Figure 3. A) Incidence of treatment adherence and B) treatment discontinuations due to adverse events[a] or lack of efficacy (safety set).[b]

PAC-SYM

- No statistically significant changes from baseline were observed in the mean PAC-SYM score in either treatment group of the full analysis set (LOCF; **Figure 4**)
  - The least-squares mean difference (97.5% CI) for the PAC-SYM total score was –0.14 (–0.44, 0.16); *P* <0.001)
  - The test statistic of the inverse normal method (5.601) exceeded the appropriate critical value (3.935) at stage 1 of the 3-stage group-sequential design, indicating that the change in constipation symptoms observed with tapentadol PR was non-inferior to that observed with oxycodone/naloxone PR

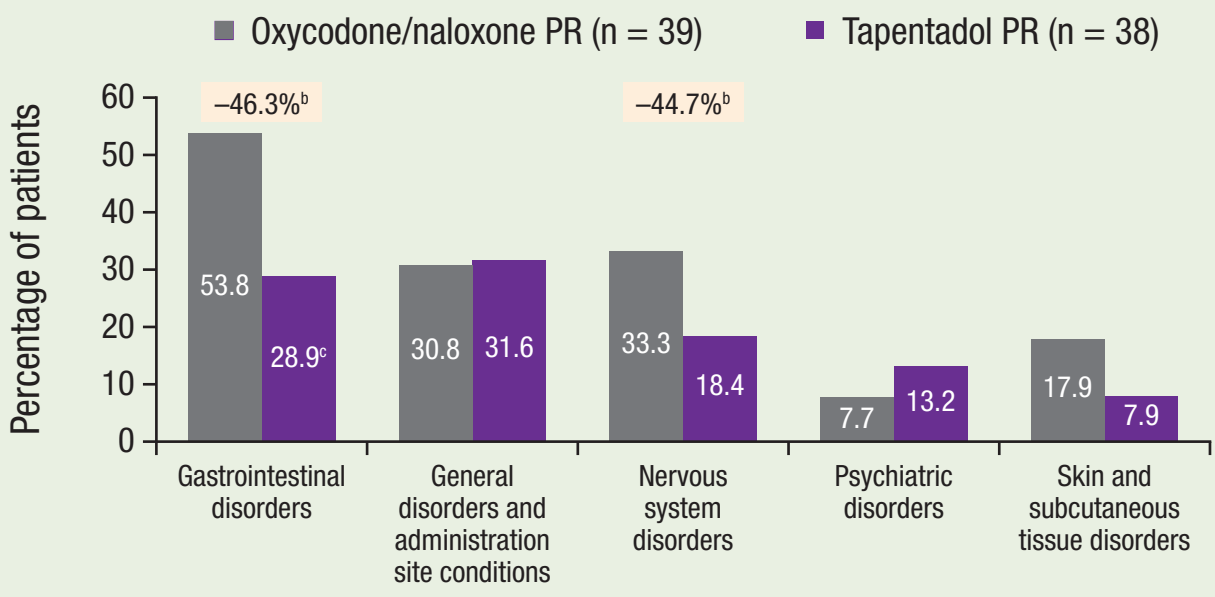


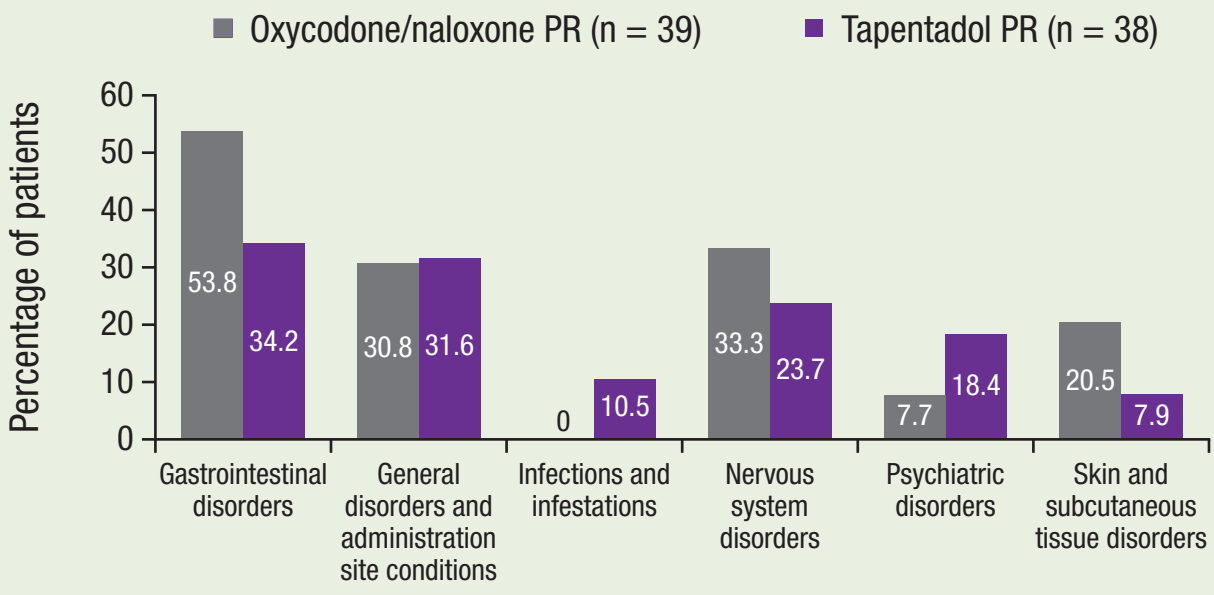
PAC-SYM, Patient Assessment of Constipation Symptoms; LS, least-squares; LOCF, last observation carried forward; PR prolonged release.
[a]Non-inferiority.
[b]Least-squares means and *P* values are obtained from an analysis of covariance model that includes treatment and pooled centers as factors and score at randomization (baseline) as a covariate.
[c]*P* <0.001 (non-inferiority; tapentadol PR vs oxycodone/naloxone PR).

Figure 4. Mean PAC-SYM total score at baseline and Week 12 and change in the PAC-SYM total score from baseline to final evaluation (LS mean; LOCF; full analysis set).

TEAEs

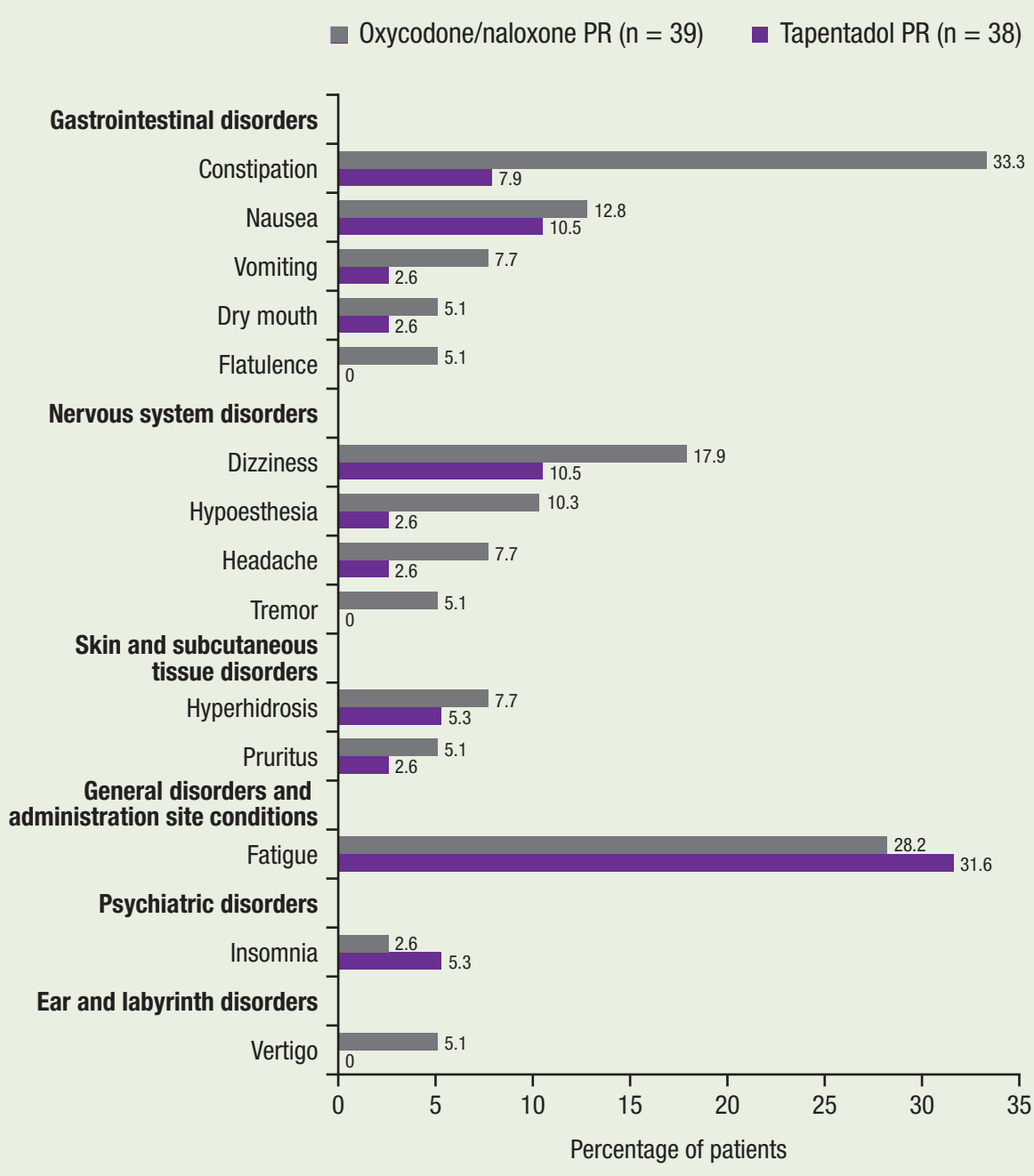
- During the titration period, the overall incidence of TEAEs was 63.2% (24/38) in the tapentadol PR group and 71.8% (28/39) in the oxycodone/naloxone PR group of the safety set
  - System organ classes of TEAEs reported by ≥10% of patients in either treatment group during the titration period are summarized in **Figure 5A**
  - Individual TEAEs reported by ≥5% of patients in either treatment group during the titration period are summarized in **Figure 6A**
    - The incidence of gastrointestinal TEAEs overall and the incidence of constipation were significantly lower in the tapentadol PR group than in the oxycodone/naloxone PR group during titration (both *P* ≤0.05; **Figure 5A** and **Figure 7**)
    - Patients in the tapentadol PR group presented a 46.3% lower incidence of gastrointestinal TEAEs overall and a 76.3% lower incidence of constipation than those in the oxycodone/naloxone PR group





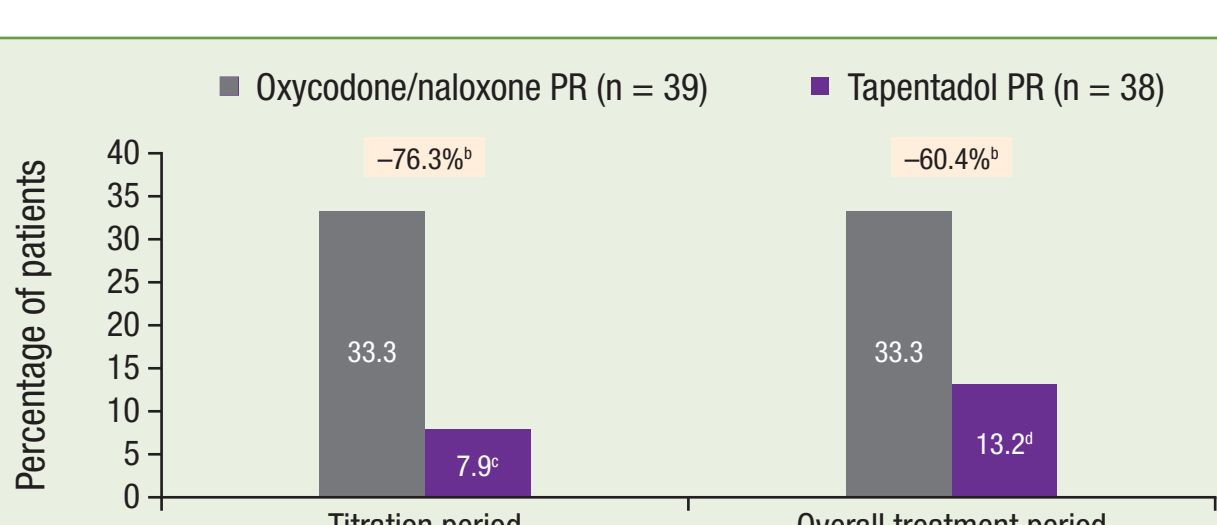
TEAE, treatment-emergent adverse event; PR, prolonged release.
[a]Descriptive analyses.
[b]Percent differences between tapentadol PR and oxycodone/naloxone PR, using oxycodone/naloxone PR as the base (denominator).
[c]*P* = 0.0267 versus oxycodone/naloxone PR.

Figure 5. System organ classes of TEAEs reported by ≥10% of patients in either treatment group during A) the titration period and B) the overall treatment period (safety set).[a]



TEAE, treatment-emergent adverse event; PR, prolonged release.

Figure 6. Individual TEAEs reported by ≥5% of patients in either treatment group in the titration period (safety set).



PR, prolonged release.
[a]Descriptive analyses.
[b]Percent difference between tapentadol PR and oxycodone/naloxone PR, using oxycodone/naloxone PR as the base (denominator).
[c]*P* = 0.0059 versus oxycodone/naloxone PR.
[d]*P* = 0.0365 versus oxycodone/naloxone PR.

Figure 7. Incidence of constipation during the titration period and the overall treatment period (safety set).[a]

- During the entire study period, the overall incidence of TEAEs was 73.7% (28/38) in the tapentadol PR group and 82.1% (32/39) in the oxycodone/naloxone PR group of the safety set
  - System organ classes of TEAEs reported by ≥10% of patients in either treatment group during the overall treatment period are summarized in **Figure 5B**, and individual TEAEs reported by ≥5% of patients in either treatment group during the overall treatment period are summarized in **Figure 6B**
    - The incidence of constipation was 60% lower in the tapentadol PR group than in the oxycodone/naloxone PR group during the overall study (**Figure 6B** and **Figure 7**)

CONCLUSIONS

- **For the second primary endpoint in this interim analysis, a low impact on bowel function (based on the PAC-SYM) was observed in both treatment groups, with a numerically better outcome for tapentadol PR**
- **Both tapentadol PR and oxycodone/naloxone PR were well tolerated**
  - **Tapentadol PR was associated with 60% less constipation than oxycodone/naloxone PR during the overall treatment period**
  - **In addition, tapentadol PR was associated with a lower incidence of both gastrointestinal TEAEs overall and constipation during the titration period compared with oxycodone/naloxone PR**
- **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**
- **Taken together, results of the current interim analysis indicate that tapentadol PR presents a favorable tolerability profile, with improved gastrointestinal tolerability compared with oxycodone/naloxone PR**

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