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ORIGINAL RESEARCH

Efficacy and Safety of Tapentadol Prolonged Release for Chronic Osteoarthritis Pain and Low Back Pain

Bernd Lange · Brigitte Kuperwasser · Akiko Okamoto · Achim Steup · Thomas Häufel · Judy Ashworth · Mila Etropolski

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ABSTRACT

Introduction: This pooled analysis of data from three phase 3 studies in patients with chronic osteoarthritis knee or low back pain evaluated the efficacy and tolerability of tapentadol prolonged release (PR; 100-250 mg twice daily) compared with placebo and oxycodone hydrochloride (HCl) controlled release (CR; 20-50 mg twice daily). ***Methods:*** Patients in each study were randomized to receive twice-daily doses of placebo, tapentadol PR (100-250 mg), or oxycodone HCl CR (20-50 mg) for a 12-week maintenance period, preceded by a 3-week titration period. Primary endpoints were change from baseline in average pain intensity (11-point numeric rating scale) at week 12 of the maintenance period and for the overall maintenance period using last observation carried forward for imputation of values missing after treatment discontinuation. ***Results:*** A total of 2968 patients were evaluated for efficacy; 2974 patients were evaluated for safety. Compared with placebo, treatment with tapentadol PR or oxycodone CR resulted in significantly greater reductions in pain intensity from baseline at week 12 and for the overall maintenance period (all $P<0.001$). For both primary endpoints, the efficacy of tapentadol PR was noninferior to oxycodone CR ($P<0.001$), and tapentadol PR had superior gastrointestinal tolerability compared with oxycodone CR ($P<0.001$). Results of analyses of responders, patient global impression of change, Short Form-36 domains (except general health), and the EuroQol 5-Dimension health status index were significantly better for tapentadol PR than oxycodone CR (all $P\leq0.048$); these results may have been affected by the worse tolerability profile of oxycodone CR. A higher percentage of patients discontinued treatment with oxycodone CR (61.7% [616/999]) compared with tapentadol PR (43.5% [425/978]). ***Conclusion:*** Tapentadol PR (100-250 mg twice daily) was efficacious and provided efficacy that was similar to oxycodone HCl CR (20-50 mg twice daily) for the management of chronic osteoarthritis knee and low back pain, with a

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superior gastrointestinal tolerability profile and fewer treatment discontinuations.

Keywords: chronic pain; EQ-5D; low back pain; opioid responder rates; opioid tolerability; osteoarthritis; oxycodone controlled release; quality of life; tapentadol prolonged release; SF-36; treatment discontinuation

INTRODUCTION

Prolonged-release formulations of opioid analgesics, such as oxycodone controlled release, provide effective relief for chronic low back pain[1-5] and osteoarthritis pain.[6-8] However, oxycodone and other mu-opioid agonists are associated with a high incidence of gastrointestinal side effects, including nausea, vomiting, and constipation, that may lead to poor patient adherence to therapy.[9] Constipation is the most common side effect associated with long-term mu-opioid use (affecting up to 95% of patients), rarely improves with prolonged therapy,[10] and often leads patients to miss or decrease opioid doses or discontinue opioid treatment.[11]

Tapentadol is a centrally acting analgesic with two mechanisms of action: mu-opioid receptor agonism and norepinephrine reuptake inhibition in a single molecule.[12,13] The combination of these two mechanisms of action may contribute to both the analgesic effect of tapentadol and the reduction in the occurrence of the side effects associated with mu-opioid agonists.[13] Tapentadol immediate release is approved in the US for the relief of moderate to severe acute pain in patients aged 18 years and older. The efficacy and tolerability of a prolonged-release formulation of tapentadol (100-250 mg twice daily) for moderate to severe chronic pain have been shown in studies in patients with osteoarthritis knee pain[14] and low back pain.[15] Due to the similarity in study design, data from three studies in patients with osteoarthritis knee pain[14] (and NCT00486811) and low back pain[15] were pooled for this analysis of the efficacy and tolerability of tapentadol prolonged release for the management of chronic pain. This pooled analysis was performed to establish the efficacy and tolerability of tapentadol prolonged release in a large patient population suffering from chronic nociceptive pain due to two different pain conditions, painful knee osteoarthritis and low back pain, and to allow a more detailed evaluation of secondary endpoints, for which the individual studies were not powered.

MATERIALS AND METHODS

Patient Population

For the three studies included in this analysis, the eligible population included men and nonpregnant, nonlactating women who had a clinical diagnosis of osteoarthritis knee pain (two studies; ClinicalTrials.gov Identifiers NCT00421928[14] and NCT00486811) or nonmalignant low back pain (one study; ClinicalTrials.gov Identifier NCT00449176[15]) for at least 3 months, had been taking analgesics for the pain condition for at least 3 months, and were dissatisfied with their current analgesic therapy. Patients on opioid therapy were required to take total daily doses of opioids equivalent to 160 mg or less of oral morphine. All patients signed an informed consent document indicating that they understood the purpose and procedures of the study and were willing to participate in the study. In all three studies, eligible patients were required to have an average pain intensity score at baseline of ≥5 on an 11-point numerical rating scale (NRS; 0="no pain" to 10="pain as bad as you can imagine").

In all three studies, patients were excluded from participation if they had a history

of alcohol or drug abuse, significant liver insufficiency, chronic hepatitis B or C, human immunodeficiency virus, malignancy within 2 years of screening (except for successfully treated basal cell carcinoma), hypersensitivity or contraindication to oxycodone or acetaminophen (or their ingredients), seizure disorder, stroke, transient ischemic attack, brain neoplasm, traumatic brain injury, uncontrolled hypertension, severely impaired renal function, or other significant disease that could affect efficacy or safety assessments. Patients who required surgery at the reference joint (osteoarthritis studies) or low back area (low back pain study) within 3 months of screening or during the study were also excluded.

In all three studies included in this analysis, neuroleptics, monoamine oxidase inhibitors, serotonin norepinephrine reuptake inhibitors, tricyclic antidepressants, anticonvulsants, and antiparkinsonian drugs were prohibited within 14 days of screening and during the study to standardize the study population. Patients with diagnosed psychiatric or neurologic disorders requiring treatment could participate in the studies if they were taking medications other than those listed above and had been on a controlled, stable dose for at least 3 months prior to randomization. Corticosteroids were also prohibited during the studies and within 4 weeks to 6 months of screening, depending on the route of administration (4 weeks for oral administration, 8 weeks for intramuscular or soft tissue administration, 3 months for intra-articular administration, and 6 months for injection of depot steroids). All analgesics, with the exception of the study drug and rescue medication, were prohibited during the washout and double-blind treatment periods of all three studies.

Study Design

The three studies included in this analysis had a randomized, multicenter, double-blind, parallel-group, placebo-controlled, and active-controlled design. All three studies included five periods: a screening period of up to 14 days; a washout period, during which patients discontinued any prior analgesic therapies; a 3-week double-blind titration period; a 12-week double-blind maintenance period; and a follow-up period, consisting of a visit 4 days after the last dose of study drug and a telephone call 10 to 14 days after the last dose of study drug. Following washout, eligible patients were randomized in a 1:1:1 ratio to receive placebo, tapentadol prolonged release (100-250 mg twice daily), or oxycodone hydrochloride (HCl) controlled release (20-50 mg twice daily). Randomization was based on a computer-generated randomization schedule and was balanced by randomly permuted blocks and stratified by study center. Randomization was implemented through an interactive voice response system (IVRS) that was used to dispense blinded study drug to each patient. The randomization schedule was maintained with the IVRS, and the investigator was not provided with the randomization codes. Blinding to treatment type was not broken during the study, except when required for emergency medical treatment; if blinding was broken by the investigator for an individual patient, that patient's participation in the study was terminated; however, the data for those patients were still included in the efficacy and safety analyses.

Active treatments were initiated with doses of tapentadol prolonged release 50 mg twice daily or oxycodone HCl controlled release 10 mg twice daily for the first 3 days. For the next 4 days, doses were increased to tapentadol prolonged release 100 mg twice daily or oxycodone HCl

controlled release 20 mg twice daily, which were the minimum allowed doses for the remainder of the study. For the remainder of the titration period in each study, patients could adjust their doses under the supervision of a physician to achieve a dose providing an optimal balance of efficacy and tolerability by increasing doses in increments of tapentadol prolonged release 50 mg twice daily or oxycodone HCl controlled release 10 mg twice daily at a minimum of 3-day intervals up to the maximum allowed doses of tapentadol prolonged release 250 mg twice daily and oxycodone HCl controlled release 50 mg twice daily or decreasing their doses in decrements of tapentadol prolonged release 50 mg twice daily or oxycodone HCl controlled release 10 mg twice daily with no time restriction. During the titration period, acetaminophen ≤1000 mg per day was allowed as rescue medication except during the last 3 days. During the maintenance period, patients attempted to maintain a steady dose level of study drug, but doses could be adjusted under the supervision of a physician within the therapeutic ranges of tapentadol prolonged release 100 to 250 mg twice daily or oxycodone HCl controlled release 20 to 50 mg twice daily. Acetaminophen ≤1000 mg per day was permitted for no more than 3 days consecutively for the relief of pain unrelated to the study-specific osteoarthritis knee pain or low back pain.

Efficacy Evaluations

For this pooled analysis of data, efficacy was evaluated using the primary efficacy endpoints (change from baseline in average pain intensity [11-point NRS] at week 12 and for the overall maintenance period); responder analyses, including the distribution of patients with an improvement from baseline in pain intensity at week 12 of the maintenance period and the percentages of responders with at least a 30% and at least a 50% reduction in pain intensity at week 12 of the maintenance period; the patient global impression of change (PGIC); the Short Form-36 (SF-36) health survey[16]; and the EuroQol 5-Dimension (EQ-5D) health survey.[17] In each study, average pain intensity scores over the previous 12 hours (rated on an 11-point NRS) were recorded by patients twice daily in an electronic diary and reviewed at each study visit. On the PGIC, patients rated their overall status since beginning the study drug on a scale from 1 to 7 (1="very much improved" to 7="very much worse") at weeks 5 and 9 of the maintenance period and at endpoint. The SF-36, which was assessed at baseline, at weeks 1, 5, and 9 of maintenance, and at endpoint, evaluated patient health status in eight domains (physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health), which were scored by patients on a scale from 0 to 100 (0="poor health" to 100="good health") and two summary scales (the physical and mental component summaries). The EQ-5D health survey, which was assessed at baseline, at weeks 1, 5, and 9 of maintenance, and at endpoint, consisted of five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) that were rated by patients on a three-point scale (1="no problems", 2="some problems", 3="extreme problems"), an overall health state measure that was rated by patients on a 100 mm visual analog scale (VAS; 0="worst imaginable health state" to 100="best imaginable health state"), and a health status index, which is calculated from the individual dimensions.

Safety Evaluations

Adverse events and treatment discontinuations were monitored throughout each study. For the

pooled analysis of safety data, the adverse events were coded using the *Medical Dictionary for Regulatory Activities* (MedDRA; www.meddramsso.com/) version 11.0.

Statistical Analysis

Data from the phase 3 chronic osteoarthritis knee pain or low back pain studies were pooled for further analysis because of the similarity of their study designs; data from individual patients (rather than study-level data) were pooled for analysis. The safety and intent-to-treat (ITT) populations included randomized patients who took at least one dose of study drug. The time to treatment discontinuation was estimated using Kaplan-Meier methods and compared using a log-rank test.

To comply with diverse global regulatory requirements, two different primary endpoints were evaluated in each of the three studies and were used as the primary endpoints in this pooled analysis. In the individual studies, the change from baseline in average pain intensity at week 12 of the maintenance period was the primary endpoint for the US, and the change from baseline in average pain intensity for the overall maintenance period was the primary endpoint for the European Union and other regions. Both primary efficacy endpoints were analyzed using an analysis of covariance (ANCOVA) model that included treatment and pooled analysis center as factors and baseline pain intensity score as a covariate. In the individual studies, analysis centers were pooled if necessary until there were at least six randomized and treated patients in each pooled analysis center; the pooled center from the individual studies was used for the pooled efficacy analysis. Differences between the active treatments and placebo were assessed using the least squares mean difference (LSMD), and the last observation carried forward (LOCF) was used as the primary method of imputing missing pain intensity scores in the event of early treatment discontinuation. Sensitivity analyses were performed using multiple imputation methods to evaluate the robustness of the primary efficacy outcomes. The following imputation methods were used in the event of early treatment discontinuation for sensitivity analyses: baseline observation carried forward (BOCF); worst observation carried forward (WOCF); modified BOCF, which was a combination of LOCF and BOCF that used the LOCF to impute missing pain intensity scores for patients with a rating of "much improved" or "very much improved" on the PGIC and the BOCF to impute missing pain intensity scores for patients with any other rating on the PGIC; and placebo mean imputation (PMI), which used the mean of all pain intensity scores for patients in the placebo group who completed treatment to impute missing pain intensity scores for patients in all treatment groups.

Secondary efficacy evaluations for the three individual studies and this pooled analysis included the distribution of responders, the percentages of patients who responded with at least a 30% and at least a 50% reduction in pain intensity at week 12 of the maintenance period, the PGIC, the SF-36 health survey,[16] and the EQ-5D health survey.[17] For the responder analysis, the percentage improvement in pain intensity from baseline to week 12 of the maintenance period was calculated by expressing the change from baseline in average pain intensity at week 12 as the percentage of baseline pain intensity. Patients whose pain worsened or who discontinued treatment before the end of the 12-week maintenance period were considered nonresponders and were assigned a value of zero. The distribution of responder rates was estimated using Kaplan-Meier methods, and treatment groups were compared using a

log-rank test. Responder rates for achieving at least a 30% and at least a 50% improvement in pain intensity at week 12 of the maintenance period and PGIC assessments at the end of the maintenance period were evaluated using the Cochran-Mantel-Haenszel method. For the SF-36 health survey, two summary scale scores (the physical and mental component summary scores) were computed based on weighted combinations of the eight SF-36 domain scores. An EQ-5D health status index score between 0 and 1 (0="dead" to 1="full health") was derived by scoring the responses to the EQ-5D health survey using a utility-weighted algorithm. An ANCOVA model similar to that used for the analysis of the primary efficacy endpoints was used to evaluate all eight dimensions and the two summary scores of the SF-36 health survey and the weighted EQ-5D health status index. The LOCF was used for imputing missing values following discontinuation for PGIC ratings, the SF-36 individual dimensions and summary scores, and the EQ-5D health status index. Between-group differences (tapentadol prolonged release vs. placebo, oxycodone controlled release vs. placebo, and tapentadol prolonged release vs. oxycodone controlled release) were evaluated for all secondary endpoints.

A meta-analysis of data from the three phase 3 studies included in the pooled analysis was conducted to compare the efficacy and the gastrointestinal tolerability between tapentadol prolonged release and oxycodone controlled release. The objectives of this meta-analysis were, first, to establish the superior gastrointestinal tolerability (as indicated by a statistically significantly lower incidence of constipation) of tapentadol prolonged release compared with oxycodone controlled release in the safety population; if that was shown, a second step was to establish the noninferior efficacy (using the primary efficacy endpoints described above) of tapentadol prolonged release compared with that of oxycodone controlled release in the ITT population. A step-down approach was used, such that the second objective (comparison of efficacy) was not tested for the ITT population unless the first objective (superior gastrointestinal tolerability for tapentadol prolonged release vs. oxycodone controlled release) was shown for the safety population. A Cochran-Mantel-Haenszel test stratified by study was used to evaluate the incidence of constipation. An inferential ANCOVA model for treatment differences that used the change in pain intensity from baseline as the response and had explanatory factors for treatment, baseline pain intensity, and study was used to evaluate efficacy; between-group differences were assessed using the LSMD. The method of Hauschke and Pigeot[18] was used to establish the noninferiority of the efficacy of tapentadol prolonged release compared with that of oxycodone controlled release by testing the noninferiority hypothesis of 50% retention of the oxycodone controlled release effect, assuming that oxycodone controlled release had superior efficacy to placebo.

RESULTS

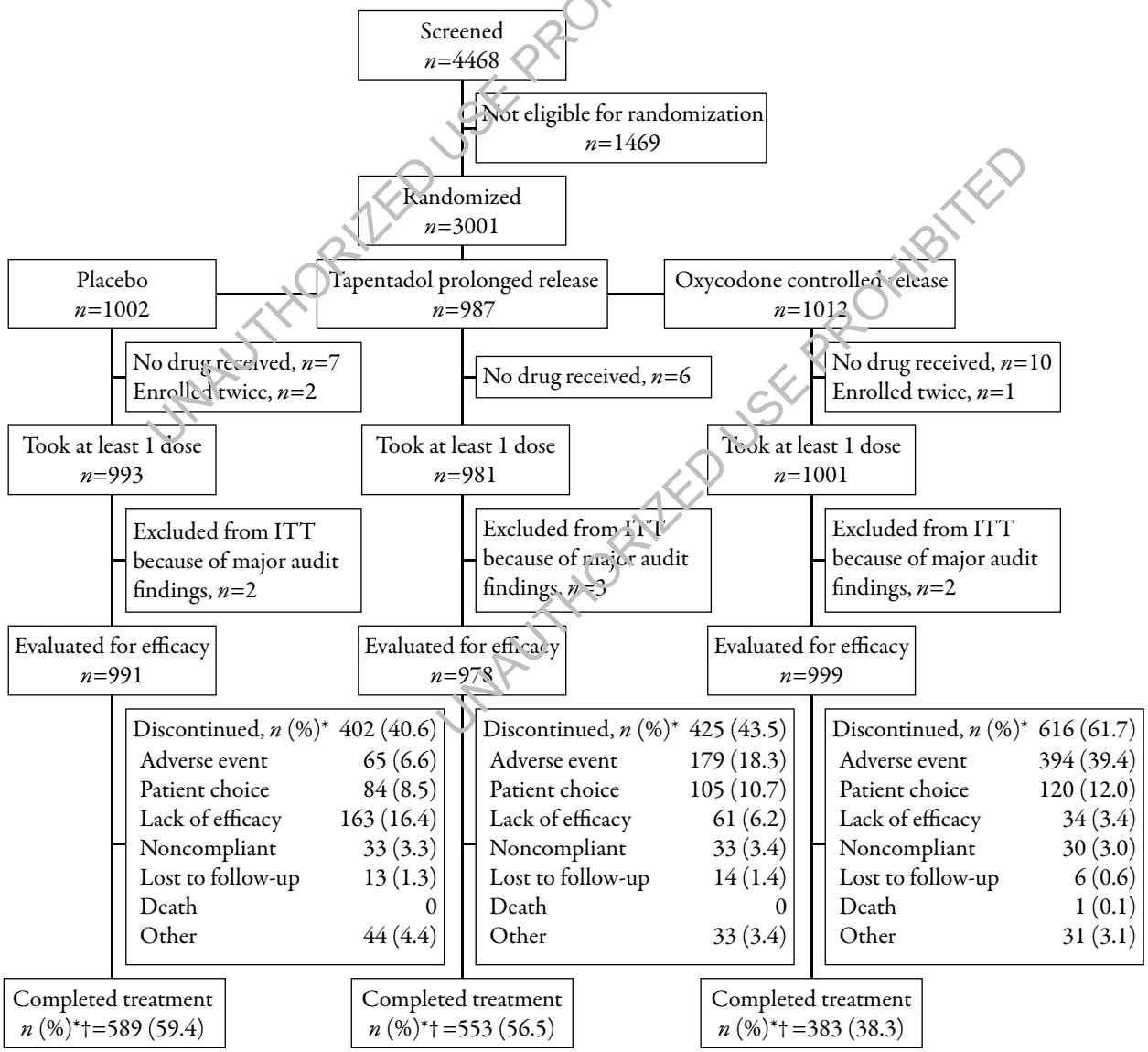
Patients

A total of 2974 patients (placebo, *n*=993; tapentadol prolonged release, *n*=980; oxycodone controlled release, *n*=1001) were evaluable for safety. The ITT population included 2968 patients (placebo, *n*=991; tapentadol prolonged release, *n*=978; oxycodone controlled release, *n*=999). The progression of patients through the studies is shown in Figure 1. Seven patients at study sites with major audit findings were excluded from the ITT population in the low back pain study and in this pooled analysis. One patient who entered both the low

back pain study[15] and a separate 1-year safety study[19] was not included in the descriptive safety analysis (because in an integrated analysis of safety database, which was the basis for the descriptive safety analysis, data from the 1-year safety study were already included for this patient) but was included in the ITT population. However, the statistical testing of adverse event incidences between tapentadol prolonged release and oxycodone controlled release was performed on the safety population from an integrated analysis of efficacy database in which this patient was included. Baseline and demographic characteristics were similar across treatment groups (Table 1).

In the placebo, tapentadol prolonged release, and oxycodone controlled release groups, respectively, 40.6% (402/991), 43.5% (425/978),

Figure 1. Patient disposition. ITT=intent-to-treat. *Percentages were calculated using the number of patients evaluated for efficacy (ITT population) as the denominator. †Included patients who enrolled in an open-label extension study following the original low back pain or osteoarthritis studies or who completed all follow-up visits in the original low back pain or osteoarthritis studies.



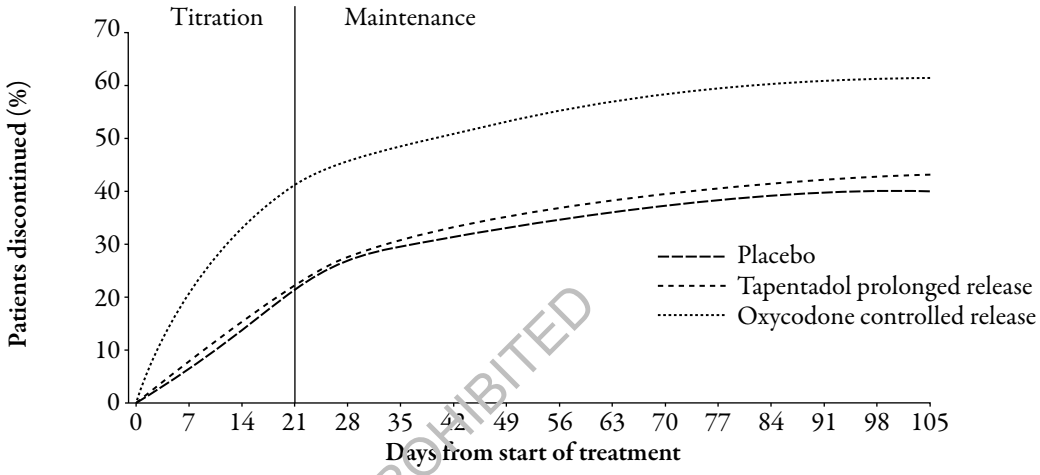
and 61.7% (616/999) of patients discontinued treatment (Figure 1). Adverse events were the most common reason for treatment discontinuation in the active treatment groups (placebo, 6.6% [65/991]; tapentadol prolonged release, 18.3% [179/978]; oxycodone controlled release, 39.4% [394/999]), while a lack of efficacy was the most common reason for treatment discontinuation in the placebo group (placebo, 16.4% [163/991]; tapentadol prolonged release, 6.2% [61/978]; oxycodone controlled release, 3.4% [34/999]). Based on Kaplan-Meier estimates, patients who received oxycodone controlled release discontinued treatment significantly earlier than patients who received placebo or tapentadol prolonged release ($P<0.001$ for both comparisons; Figure 2). The median time to treatment discontinuation was 124.0 days in the placebo group, 118.0 days in the tapentadol prolonged release group,

Table 1. Demographic and baseline characteristics (intent-to-treat population).

Characteristic	Placebo (*n*=991)	Tapentadol prolonged release (*n*=978)	Oxycodone controlled release (*n*=999)
Mean±SD age, years	57.0±12.03	56.8±12.22	56.7±12.39
Age category, *n* (%):			
<65 years	718 (72.5)	719 (73.5)	731 (73.2)
≥65 years	273 (27.5)	259 (26.5)	268 (26.8)
Gender, *n* (%):			
Female	640 (64.6)	639 (65.3)	601 (60.2)
Male	351 (35.4)	339 (34.7)	398 (39.8)
Race, *n* (%)*:			
White	837 (84.5)	803 (82.1)	813 (81.4)
Black	88 (8.9)	111 (11.3)	101 (10.1)
Hispanic	41 (4.1)	40 (4.1)	58 (5.8)
Other	25 (2.5)	24 (2.5)	27 (2.7)
Pain condition, *n* (%):			
Osteoarthritis knee pain	674 (68.0)	663 (67.8)	673 (67.4)
Low back pain	317 (32.0)	315 (32.2)	326 (32.6)
Mean±SD pain intensity score†‡	7.4±1.25	7.4±1.26	7.3±1.21
Pain intensity category,‡§ *n* (%):			
Mild	0	2 (0.2)	0
Moderate	143 (14.5)	119 (12.2)	123 (12.3)
Severe	845 (85.5)	854 (87.6)	873 (87.7)
Prior opioid experience,◊ *n* (%):			
No	649 (65.5)	641 (65.5)	681 (68.2)
Yes	342 (34.5)	337 (34.5)	318 (31.8)

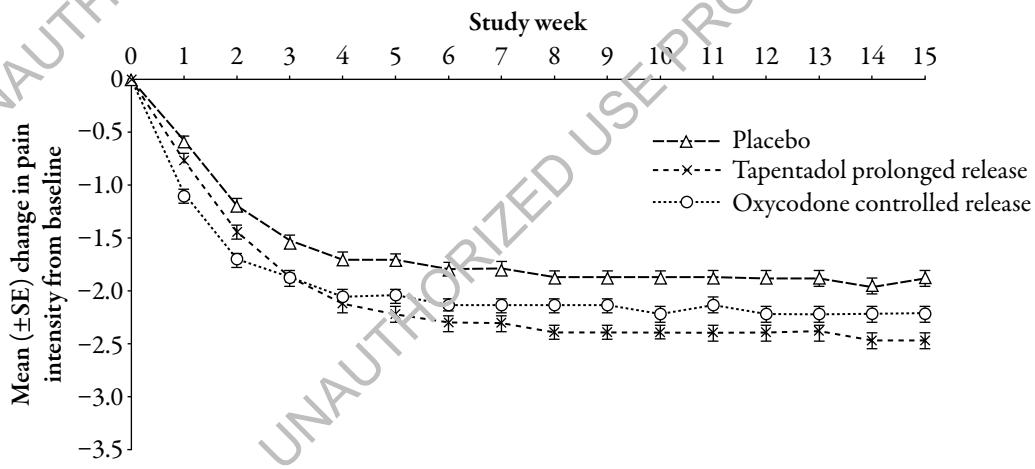
*Percentages may not total 100% because of rounding.
†Baseline pain intensity was the average of pain scores (11-point numerical rating scale) recorded over the last 72 hours prior to randomization.
‡Placebo, *n*=988; tapentadol prolonged release, *n*=975; oxycodone controlled release, *n*=996.
§Mild pain intensity was defined as a rating of 1 to <4 on the numerical rating scale; moderate was defined as a rating of ≥4 to <6, and severe was defined as a rating of ≥6.
◊Prior opioid experience was defined as having taken opioid analgesics during the 3 months prior to screening.

Figure 2. Time to treatment discontinuation (intent-to-treat population). DB=double blind; Vertical line=end of the titration period (21 days).



Number of patients remaining in DB without an event																
Placebo	991	929	865	789	731	702	675	661	644	637	626	617	610	603	589	392
Tapentadol prolonged release	978	913	828	764	714	681	658	638	618	606	589	583	578	568	560	364
Oxycodone controlled release	999	782	666	587	537	510	491	475	446	432	422	418	403	393	385	251

Figure 3. Mean change from baseline in average pain intensity over time using the last observation carried forward (intent-to-treat population).



and 39.0 days in the oxycodone controlled release group.

Efficacy

Reductions from baseline in average pain intensity over the double-blind treatment period were observed for all three treatment groups. The change from baseline in average pain intensity over time is shown in Figure 3. Compared with placebo, statistically significant reductions from baseline in average pain intensity were observed with tapentadol prolonged release at both week 12 of the maintenance period (LSMD vs.

placebo –0.6, 95% CI: –0.80, –0.39; *P*<0.001) and for the overall maintenance period (–0.5, 95% CI: –0.73, –0.34; *P*<0.001). Statistically significant reductions from baseline in average pain intensity were also observed with oxycodone controlled release compared with placebo at both week 12 of the maintenance period (LSMD vs. placebo –0.3, 95% CI: –0.53, –0.12; *P*=0.002) and for the overall maintenance period (–0.3, 95% CI: –0.52, –0.14; *P*<0.001).

Sensitivity analyses showed that tapentadol prolonged release significantly reduced average pain intensity from baseline to week 12 of the maintenance period and for the overall maintenance period compared with placebo using alternative imputation methods, including the more conservative BOCF and WOCF, as well as the modified BOCF and the PMI (*P*≤0.015 for all comparisons; Figure 4A). Compared with placebo, oxycodone controlled release showed significant reductions in average pain intensity from baseline to week 12 of the maintenance period using the PMI (*P*<0.001), but not the BOCF (*P*=0.002, in favor of placebo), the WOCF (*P*=0.001, in favor of placebo), or the modified BOCF (*P*=0.176; Figure 4A). Oxycodone controlled release also significantly reduced average intensity from baseline for the overall maintenance period compared with placebo using the PMI (*P*<0.001), but not the BOCF (*P*=0.008, in favor of placebo), the WOCF (*P*=0.003, in favor of placebo), or the modified BOCF (*P*=0.141; Figure 4B).

The overall distribution of responders at week 12 of the maintenance period was significantly different between the tapentadol prolonged release and placebo groups (*P*=0.006) and the tapentadol prolonged release and oxycodone controlled release groups (*P*<0.001), with a higher percentage of responders in the tapentadol prolonged release group than in the placebo or oxycodone controlled release groups (Figure 5). A significant difference was also observed in the distribution of responder rates between oxycodone controlled release and placebo (*P*=0.023), in favor of placebo (Figure 5). A significantly higher percentage of patients in the tapentadol prolonged release group showed at least a 30% improvement in pain intensity from baseline to week 12 of the maintenance period compared with placebo (41.3% [404/978] vs. 34.8% [345/991]; *P*=0.003), while a significantly lower percentage of patients in the oxycodone controlled release group showed at least a 30% improvement in pain intensity from baseline to week 12 compared with placebo (27.0% [270/999]; *P*<0.001). A significantly higher percentage of patients in the tapentadol prolonged release group showed at least a 50% improvement in pain intensity from baseline to week 12 compared with placebo (30.1% [294/978] vs. 23.5% [233/991]; *P*<0.001), but no significant difference versus placebo was observed in the percentage of patients who received oxycodone controlled release (20.8% [208/999]; *P*=0.153). A significantly higher percentage of patients in the tapentadol prolonged release group achieved at least a 30% and at least a 50% improvement in pain intensity from baseline to week 12 compared with the oxycodone controlled release group (*P*<0.001 for both comparisons).

On the PGIC, 37.4% (304/812) of patients in the placebo group, 56.7% (421/742) of patients in the tapentadol prolonged release group, and 49.8% (310/622) of patients in the oxycodone controlled release group reported that their overall status was "much improved" or "very much improved" at endpoint. There was a significant difference in the overall distribution of PGIC scores favoring tapentadol prolonged release and oxycodone controlled release compared with placebo (*P*<0.001 for both comparisons) and favoring tapentadol

Figure 4. Sensitivity analyses of the primary efficacy endpoints (intent-to-treat population). (**A**) Change from baseline at week 12 of the maintenance period. (**B**) Change from baseline for the overall maintenance period. BOCF=baseline observation carried forward; LOCF=last observation carried forward; PMI=placebo mean imputation; WOCF=worst observation carried forward.

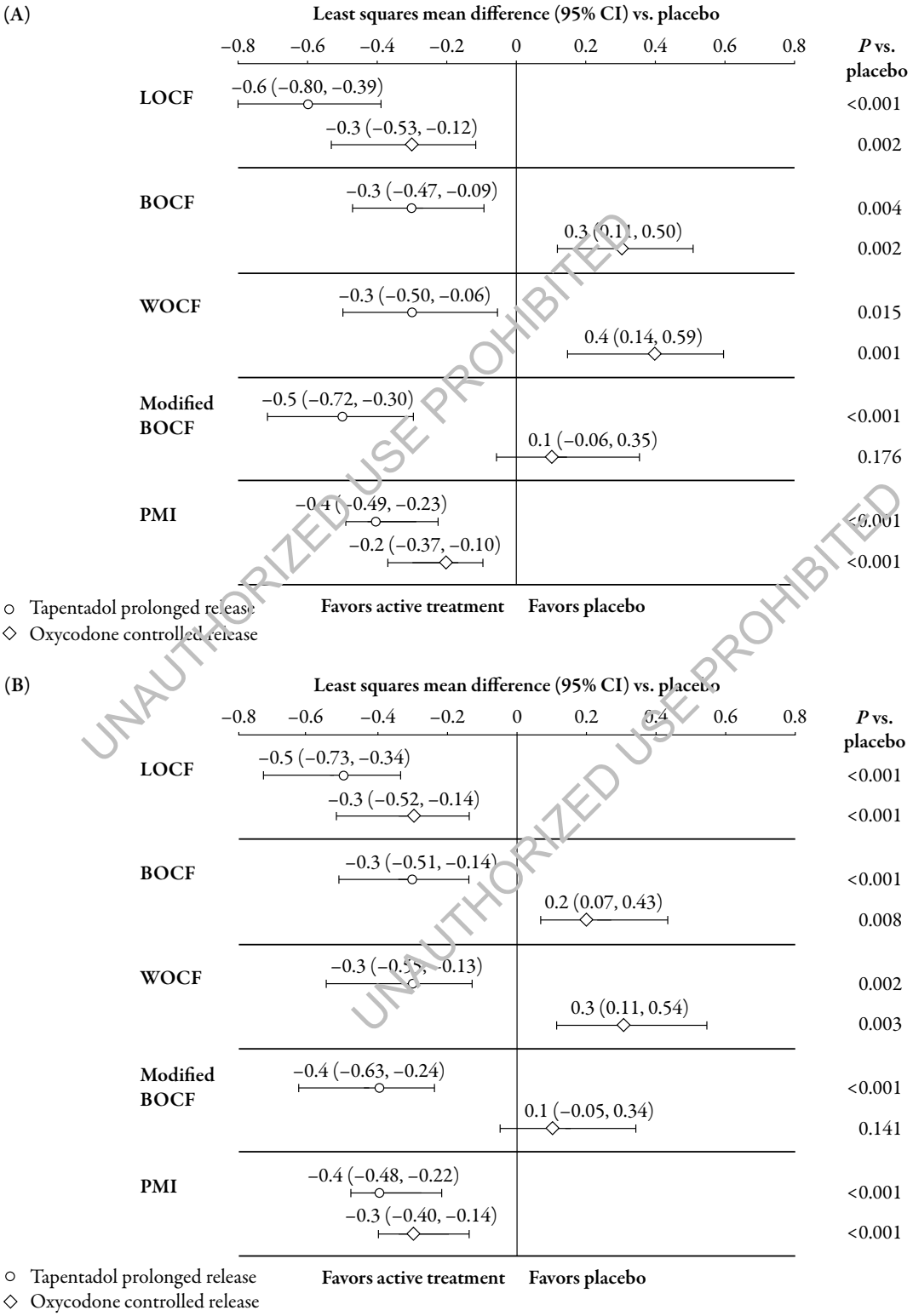
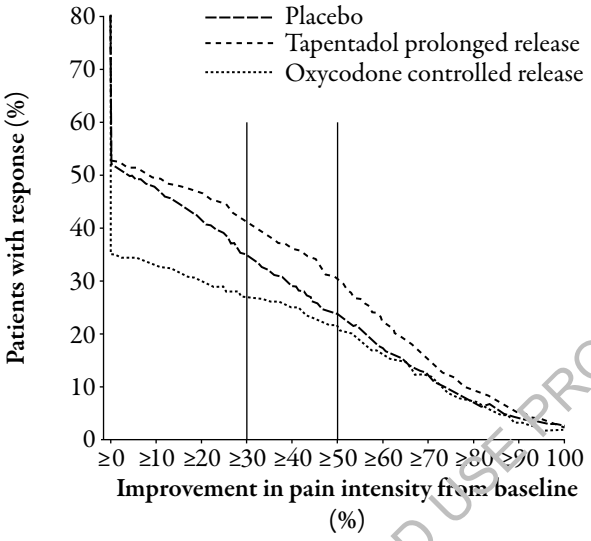


Figure 5. Responder rates at week 12 of the maintenance period (intent-to-treat population). Patients who discontinued early or worsened were considered non-responders. Vertical lines=thresholds of ≥30% and ≥50% improvement in pain intensity, respectively.



prolonged release over oxycodone controlled release (P<0.001; Figure 6).

On the SF-36 questionnaire, significant improvements from baseline to endpoint were observed with tapentadol prolonged release compared with placebo in the physical functioning, role-physical, bodily pain, and vitality scores (P<0.041 for all comparisons; Table 2). A significant improvement from baseline to endpoint was also observed in the physical component summary score compared with placebo (P<0.001). At endpoint, no significant improvements from baseline were observed in any of the SF-36 domain or summary scores with oxycodone controlled release compared with placebo; however, statistically significant differences favoring placebo over oxycodone controlled release were shown for the vitality, social functioning, mental health, and mental component summary scores (P≤0.004 for all comparisons; Table 2). Tapentadol prolonged release was also associated with significantly greater improvements from baseline to endpoint

Figure 6. Patient global impression of change at endpoint (intent-to-treat population).

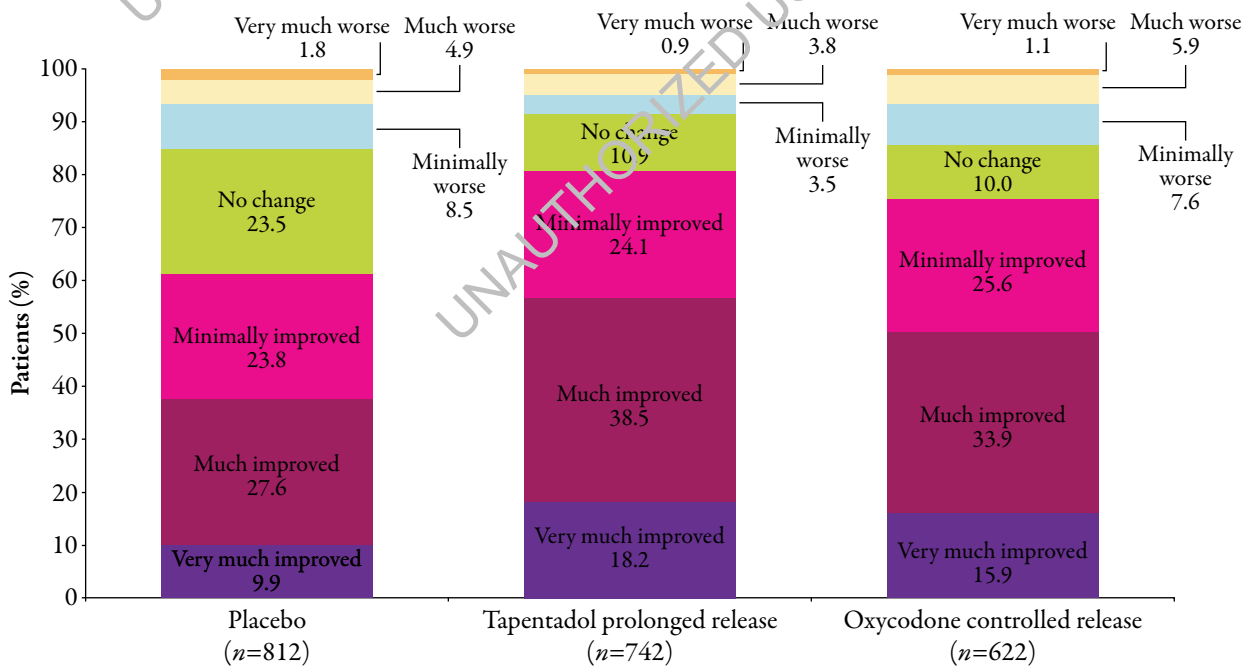


Table 2. Results of the SF-36 health status questionnaire at endpoint (intent-to-treat population).

	Tapentadol prolonged release		Oxycodone controlled release	
SF-36 endpoint	LSMD vs. placebo (95% CI)	*P* vs. placebo	LSMD vs. placebo (95% CI)	*P* vs. placebo
Physical functioning	3.4 (1.70, 5.19)	<0.001	1.1 (−0.67, 2.81)	0.226
Role-physical	5.3 (2.07, 8.43)	0.001	−0.6 (−3.74, 2.60)	0.723
Bodily pain	4.5 (2.80, 6.28)	<0.001	0.8 (−0.95, 2.52)	0.375
General health	0.1 (−1.06, 1.25)	0.871	−1.0 (−2.15, 0.14)	0.087
Vitality	1.6 (0.07, 3.13)	0.041	−2.8 (−4.33, −1.27)	<0.001*
Social functioning	1.6 (−0.21, 3.47)	0.083	−2.7 (−4.50, −0.83)	0.004*
Role-emotional	0.4 (−2.76, 3.50)	0.817	−2.8 (−5.89, 0.34)	0.081
Mental health	−1.1 (−2.40, 0.27)	0.118	−2.8 (−4.15, −1.49)	<0.001*
Physical component summary	1.9 (1.21, 2.65)	<0.001	0.6 (−0.13, 1.30)	0.108
Mental component summary	−0.6 (−1.34, 0.23)	0.167	−1.9 (−2.68, −1.11)	<0.001*

*Indicates statistically significant worsening compared with placebo.
LSMD=least squares mean difference; SF-36=Short Form-36.

Table 3. EQ-5D scores: mean baseline scores and changes from baseline to endpoint.

	Placebo (*n*=990)		Tapentadol prolonged release (*n*=978)		Oxycodone controlled release (*n*=998)	
EQ-5D measure	Mean baseline score	Mean (SE) change from baseline to endpoint	Mean baseline score	Mean (SE) change from baseline to endpoint	Mean baseline score	Mean (SE) change from baseline to endpoint
Mobility*†	1.9	−0.1 (0.01)	1.9	−0.2 (0.01)	1.9	−0.1 (0.01)
Self-care*‡	1.3	−0.0 (0.01)	1.3	−0.1 (0.01)	1.3	−0.0 (0.01)
Usual activities*	1.9	−0.1 (0.02)	1.9	−0.2 (0.02)	1.9	−0.1 (0.02)
Pain/discomfort*‡	2.4	−0.3 (0.02)	2.4	−0.4 (0.02)	2.4	−0.3 (0.02)
Anxiety/depression*	1.5	−0.1 (0.02)	1.5	−0.1 (0.02)	1.4	−0.0 (0.02)
Health status index§	0.4	0.1 (0.01)	0.4	0.2 (0.01)#**	0.4	0.1 (0.01)
Health state (VAS)◊¶	59.6	5.5 (0.97)	59.4	8.0 (0.68)	60.6	5.1 (0.63)

*Scores on individual dimensions, which were rated by patients on a three-point scale (1="no problems", 2="some problems", 3="extreme problems").
†Placebo, *n*=990; tapentadol prolonged release, *n*=978; oxycodone controlled release, *n*=997.
‡Placebo, *n*=989; tapentadol prolonged release, *n*=978; oxycodone controlled release, *n*=998.
§Health status index score between 0 and 1 (0="dead" to 1="full health") was derived by scoring the responses to the EQ-5D health survey using a utility-weighted algorithm.
◊Health state score, which was rated by patients on a 100-mm VAS.
¶Placebo, *n*=988; tapentadol prolonged release, *n*=978; oxycodone controlled release, *n*=997.
#*P*<0.001 versus placebo.
**$P<0.001$ versus oxycodone controlled release.
EQ-5D=EuroQol 5-Dimension; SE=standard error; VAS=visual analog scale.

compared with oxycodone controlled release for all individual domain scores except general health ($P \leq 0.048$ for all comparisons), as well as for the physical component summary (LSMD between tapentadol prolonged release and oxycodone controlled release –1.3, 95% CI: –2.06, –0.63; $P<0.001$) and the mental component summary (–1.3, 95% CI: –2.12, –0.56; $P<0.001$).

On the EQ-5D questionnaire, a significantly greater improvement from baseline to endpoint was observed in the health status index score with tapentadol prolonged release compared with placebo (LSMD vs. placebo 0.0, 95% CI: 0.02, 0.07; $P<0.001$); the difference between oxycodone controlled release and placebo was not statistically significant (–0.0, 95% CI: –0.02, 0.02; $P=0.867$). A significantly greater improvement from baseline to endpoint in the health status index score was also observed with tapentadol prolonged release compared with oxycodone controlled release (LSMD between tapentadol prolonged release and oxycodone controlled release –0.0, 95% CI: –0.07, –0.02; $P<0.001$). The changes from baseline in the individual dimensions, as well as the health state (VAS) and health status index scores, are shown in Table 3.

Safety

The most common treatment-emergent adverse events (TEAEs) in the safety population (incidence ≥5% in any treatment group) were nausea, dizziness, constipation, headache, somnolence, fatigue, vomiting, dry mouth, hyperhidrosis, pruritus, and diarrhea (Table 4). The overall incidence of gastrointestinal disorders was statistically significantly lower in the tapentadol prolonged release group (42.8% [420/981]) compared with the oxycodone

Table 4. Treatment-emergent adverse events , *n* (%), reported by at least 5% of patients in any treatment group (safety population)*.

SOC or preferred term for TEAE	Placebo (*n*=993)	Tapentadol prolonged release (*n*=980)	Oxycodone controlled release (*n*=1001)
Gastrointestinal disorders	264 (26.6)	420 (42.9)	657 (65.6)
Nausea	73 (7.4)	203 (20.7)	362 (36.2)
Constipation	69 (6.9)	166 (16.9)	330 (33.0)
Vomiting	29 (2.9)	80 (8.2)	210 (21.0)
Dry mouth	22 (2.2)	67 (6.8)	40 (4.0)
Diarrhea	58 (5.8)	51 (5.2)	51 (5.1)
Nervous system disorders	223 (22.5)	394 (40.2)	463 (46.3)
Dizziness	63 (6.3)	169 (17.2)	210 (21.0)
Headache	131 (13.2)	146 (14.9)	132 (13.2)
Somnolence	35 (3.5)	114 (11.6)	168 (16.8)
General disorders and administration-site conditions	105 (10.6)	174 (17.8)	198 (19.8)
Fatigue	39 (3.9)	83 (8.5)	92 (9.2)
Skin and subcutaneous tissue disorders	50 (5.0)	132 (13.5)	237 (23.7)
Hyperhidrosis	9 (0.9)	52 (5.3)	60 (6.0)
Pruritus	16 (1.6)	51 (5.2)	134 (13.4)

*Incidence is based on the number of patients experiencing ≥1 TEAE, not the number of events.
SOC=system organ class; TEAE=treatment-emergent adverse event.

controlled release group (65.6% [657/1001]; $P<0.001$). The incidence of nervous system disorders was numerically lower in the tapentadol prolonged release group (40.2% [394/980]) compared with the oxycodone controlled release group (46.3% [463/1001]), as was the incidence of skin and subcutaneous disorders (13.5% [132/980] vs. 23.7% [237/1001]), particularly pruritus (5.2% [51/980] vs. 13.4% [134/1001]).

Comparison of Tapentadol Prolonged Release and Oxycodone Controlled Release

The incidences of specific gastrointestinal TEAEs were statistically significantly lower in the tapentadol prolonged release group compared with the oxycodone controlled release group, including the incidences of constipation (16.9% [166/981] vs. 33.0% [330/1001]; $P<0.001$), nausea (20.7% [203/981] vs. 36.2% [362/1001]; $P<0.001$), vomiting (8.2% [80/981] vs. 21.0% [210/1001]; $P<0.001$), and the composite of nausea and vomiting (23.3% [229/981] vs. 42.7% [427/1001]; $P<0.001$). The times to the first occurrence of constipation, nausea, vomiting, and the composite of nausea and vomiting were all significantly longer in the tapentadol prolonged release group compared with the oxycodone controlled release group ($P<0.001$ for all comparisons).

According to the conditions of the noninferiority meta-analysis, the noninferiority of the efficacy of tapentadol prolonged release compared with that of oxycodone controlled release was evaluated because the gastrointestinal tolerability profile of tapentadol prolonged release was superior to that of oxycodone controlled release. A required condition of the Hauschke and Pigeot[18] method of analysis was met because oxycodone controlled release was significantly superior to placebo for both the change from baseline in average pain intensity at week 12 of the maintenance period and for the overall maintenance period using the LOCF ($P<0.001$ for both comparisons). Results of the noninferiority analysis demonstrated that the efficacy of tapentadol prolonged release was noninferior to that of oxycodone controlled release (using the LOCF) using both the change from baseline in average pain intensity at week 12 of the maintenance period and for the overall maintenance period (50% retention of the oxycodone controlled release effect; $P<0.001$). Furthermore, sensitivity analyses using alternative imputation methods (BOCF, WOCF, modified BOCF, and PMI) also consistently showed that the efficacy of tapentadol prolonged release was noninferior to that of oxycodone controlled release for both primary endpoints ($P<0.001$ for all comparisons).

DISCUSSION

In this pooled analysis of data from three phase 3 studies, tapentadol prolonged release (100-250 mg twice daily) was effective for the management of moderate to severe chronic pain. Pain intensity levels were statistically significantly improved with tapentadol prolonged release (100-250 mg twice daily) and oxycodone HCl controlled release (20-50 mg twice daily) compared with placebo at both week 12 of the maintenance period and for the overall maintenance period. Sensitivity analyses using different methods of imputing missing pain intensity scores after treatment discontinuation showed that the efficacy results were more robust for tapentadol prolonged release than for oxycodone controlled release. The higher rate of treatment discontinuations in the oxycodone controlled release group (61.7%) compared with the tapentadol prolonged release group (43.5%) may have had a negative impact on efficacy outcomes for oxycodone controlled

release, particularly when the more conservative imputation methods, such as BOCF or WOCF, were used.

The distribution of responder rates was significantly better for tapentadol prolonged release compared with both placebo and oxycodone controlled release. Significant improvements in health status measures (as measured using the SF-36 questionnaire and the EQ-5D health survey) were also shown for tapentadol prolonged release compared with both placebo and oxycodone controlled release. The results of these questionnaires indicate that health status significantly improved with treatment with tapentadol prolonged release but not with oxycodone controlled release, which may have reflected the worse tolerability profile of oxycodone controlled release compared with tapentadol prolonged release. The higher rate of treatment discontinuations in the oxycodone controlled release group compared with the tapentadol prolonged release group may have also had a negative impact on responder rates (because all patients who discontinued treatment were considered nonresponders) and on SF-36 and EQ-5D outcomes for oxycodone controlled release. The high discontinuation rate observed with oxycodone controlled release in the current analysis was not unusual; similar discontinuation rates have been observed in previous studies.[4,5,7,20] In a 90-day, randomized, placebo-controlled, flexible-dosing study[20] in 107 patients with persistent moderate to severe osteoarthritis pain, 58.9% of patients treated with oxycodone controlled release discontinued treatment compared with 61.7% in the current analysis. In a separate 4-week, randomized, placebo-controlled study[7] (n=489 dosed) comparing oxymorphone ER with oxycodone controlled release for the management of chronic osteoarthritis pain, 40.0% of patients treated with oxycodone controlled release 20 mg twice daily discontinued treatment.

In the current analysis, tapentadol prolonged release (100-250 mg twice daily) provided efficacy that was noninferior to that provided by oxycodone HCl controlled release (20-50 mg twice daily), but the incidence of select gastrointestinal adverse events (nausea, vomiting, constipation, and the composite of nausea and vomiting) was significantly lower in the tapentadol prolonged release group than in the oxycodone controlled release group, indicating that tapentadol prolonged release (100-250 mg twice daily) was at least as effective as oxycodone controlled release (20-50 mg twice daily) and that the gastrointestinal tolerability of tapentadol prolonged release (100-250 mg twice daily) was superior to that of oxycodone HCl controlled release (20-50 mg twice daily). The incidences of select gastrointestinal TEAEs associated with oxycodone controlled release in the current pooled analysis are comparable to those observed in previous phase 3 studies of oxycodone controlled release in patients with chronic low back or osteoarthritis pain.[1,7,20,21] In the previously described 90-day randomized, placebo-controlled study of oxycodone controlled release in patients with persistent moderate to severe osteoarthritis pain, the incidences of constipation, nausea, vomiting, dizziness, and somnolence were 48.2%, 41.1%, 12.5%, 32.1%, and 32.1%, respectively, compared with 33.0%, 36.2%, 21.0%, 21.0%, and 16.8%, respectively, in the current analysis. The lower incidence of gastrointestinal TEAEs with tapentadol prolonged release compared with oxycodone controlled release observed in the current pooled analysis as well as in previous studies of tapentadol prolonged release for chronic pain[14,15,19] is likely related to the dual mechanism of action (mu-opioid

receptor agonism and norepinephrine reuptake inhibition) of tapentadol.[12,13] The contribution of norepinephrine reuptake inhibition to the analgesic activity of tapentadol may decrease the activation of mu-opioid receptors that is required to achieve analgesia and lead to an opioid-sparing effect, thereby reducing the occurrence of side effects, including gastrointestinal side effects, that are related to mu-opioid receptor agonists.[12,13]

Tapentadol prolonged release (100-250 mg twice daily) was shown to be effective for the management of chronic pain and was associated with improvements in overall health status and quality of life measures in randomized, placebo-controlled and active-controlled, phase 3 studies in patients with osteoarthritis knee pain[14] (and NCT00486811) and low back pain.[15] Additionally, although no formal comparisons were made, the incidence of gastrointestinal adverse events, including nausea, vomiting, and constipation, was numerically lower with treatment with tapentadol prolonged release compared with oxycodone controlled release. The results of this pooled analysis confirm that tapentadol prolonged release effectively relieves moderate to severe chronic osteoarthritis knee pain and low back pain with an improved gastrointestinal tolerability profile and numerical improvements in the incidence of TEAEs related to the nervous system compared with oxycodone controlled release.

In previous studies in patients with chronic osteoarthritis pain and low back pain,[14,15,19] a dose conversion ratio of approximately 5:1 (50 mg tapentadol prolonged release for every 10 mg oxycodone HCl controlled release) for tapentadol prolonged release to oxycodone controlled release was demonstrated. There are no data on direct conversion from other opioids to tapentadol prolonged release; however, dose conversion data that are available in the literature can be used to calculate the relative equianalgesic dose of other opioids to oxycodone controlled release,[22] and the dose of tapentadol prolonged release can be determined using the above-mentioned dose conversion ratio of approximately 5:1 of tapentadol prolonged release to oxycodone controlled release.

Results of secondary endpoints and quality of life measures (responder analyses, the PGIC, the EQ-5D health status index, and SF-36 domains [except general health]) were better with tapentadol prolonged release than with oxycodone controlled release treatment, although the worse gastrointestinal tolerability profile associated with oxycodone controlled release may have contributed to these poorer outcomes.

CONCLUSION

Tapentadol prolonged release (100-250 mg twice daily) was efficacious and provided efficacy that was similar to oxycodone HCl controlled release (20-50 mg twice daily) for the management of chronic osteoarthritis knee and low back pain, with a superior gastrointestinal tolerability profile. It also may be particularly beneficial for patients requiring prolonged therapy for chronic pain because fewer treatment discontinuations may lead to better adherence to treatment.

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