Randomized Trial

Tapentadol Prolonged Release for Managing Moderate to Severe, Chronic Malignant Tumor-Related Pain

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Background: Tapentadol prolonged release (PR) is effective and well tolerated for chronic osteoarthritis, low back, and diabetic peripheral neuropathic pain.

Objectives: To evaluate the efficacy and tolerability of tapentadol PR compared with placebo and morphine controlled release (CR) for managing moderate to severe chronic malignant tumor-related pain.

Study Design: Randomized-withdrawal, parallel group, active- and placebo-controlled, double-blind phase 3 study (NCT00472303).

Setting: Primary, secondary, and tertiary care settings in 16 countries.

Methods: Eligible patients (pain intensity ≥ 5 [11-point numerical rating scale] on prior analgesics) were randomized (2:1) and titrated to their optimal dose of tapentadol PR (100 – 250 mg bid) or morphine sulfate CR (40 – 100 mg bid) over 2 weeks. Morphine sulfate immediate release 10 mg was permitted as needed for rescue medication (no maximum dose). Patients who completed titration and, during the last 3 days of titration, had mean pain intensity < 5 (based on twice-daily ratings) and mean rescue medication use ≤ 20 mg/day continued into a 4-week maintenance period; patients who received morphine CR during titration continued taking morphine CR, and those who received tapentadol PR were re-randomized (1:1) to tapentadol PR or placebo bid. Response during maintenance (primary efficacy endpoint) was defined as having: 1) completed the maintenance period, 2) a mean pain intensity < 5 during maintenance, and 3) used an average of ≤ 20 mg/day of rescue medication during maintenance. Response at the end of titration was defined similarly, with pain intensity and rescue medication averages based on the last 3 days of titration.

Results: Of 622 patients screened, 496 were randomized, treated during titration, and evaluable for safety; 327 were re-randomized, treated during maintenance, and evaluable for safety; and 325 were evaluable for efficacy. The adjusted responder rate estimate during maintenance (logistic regression adjusting for treatment group, pooled center, and pain intensity at start of maintenance) was significantly higher with tapentadol PR (64.3%) than with placebo (47.1%; odds ratio (OR), 2.02 [95% confidence interval (CI), 1.12 – 3.65]; $P = 0.02$). Based on responder rates at the end of titration, tapentadol PR (76.0% [174/229]) was non-inferior to morphine CR (83.0% [83/100]). The lower limit of the 95% CI for the between-groups difference (–15.5%) was within the pre-specified 20% non-inferiority margin. During titration, incidences of treatment-emergent adverse events (TEAEs) were 50.0% (169/338) with tapentadol PR and 63.9% (101/158) with morphine CR; incidences of nausea, vomiting, and dry mouth were lower with tapentadol PR than with morphine CR. During maintenance, incidences of TEAEs were 56.3% (63/112), 62.3% (66/106), and 62.4% (68/109) with placebo, tapentadol PR, and morphine CR, respectively.

Limitations: Statistical comparisons between tapentadol PR and morphine CR were limited to descriptive statistics during the maintenance period because of the pre-selection of responders to tapentadol PR or morphine CR during titration.

Conclusions: Results obtained during maintenance indicate that tapentadol PR (100 – 250 mg bid) is effective compared with placebo for managing moderate to severe chronic malignant tumor-related pain. Based on results obtained during titration, tapentadol PR provides comparable efficacy to that of morphine sulfate CR (40 – 100 mg bid), but is associated with better gastrointestinal tolerability.

Key words: Tapentadol PR, cancer pain, tumor-related pain, malignant pain, chronic pain, morphine CR, non-inferiority, efficacy, tolerability

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Chronic pain is one of the most common and distressing symptoms for patients with malignant tumors (1,2), affecting up to 75% of all patients with solid tumors (2). Chronic cancer pain is often mixed pain, with nociceptive, neuropathic, and/or visceral components that complicate pain management (2). Morphine has long been considered the analgesic of choice for the management of moderate to severe cancer pain, but is associated, like most other opioid analgesics, with a high incidence of adverse events (AEs), particularly gastrointestinal AEs (3,4). Although there is extensive clinical experience with the use of strong opioid analgesics for cancer pain, evidence of efficacy and tolerability from placebo-controlled trials is generally lacking (5). The evaluation of analgesics for cancer pain in clinical studies is challenging, due to the complexity of cancer pain (2) and to ethical concerns regarding the use of a standard placebo-controlled design. Data from controlled clinical trials could contribute to improving the management of cancer pain, which is often poorly controlled. In a survey of patients with moderate to severe cancer pain, 63% of patients who were receiving prescription analgesics (n = 441) reported that their pain relief was inadequate (6).

Tapentadol represents a new class of centrally acting analgesics, with 2 mechanisms of action: μ-opioid receptor agonism and noradrenaline reuptake inhibition (7,8). Tapentadol prolonged release (PR; extended release [ER] in the United States; 100 – 250 mg bid) has been shown to be effective and well tolerated for the management of moderate to severe chronic pain (9-13), with comparable analgesic efficacy and superior gastrointestinal tolerability to oxycodone HCl controlled release (CR; 20 – 50 mg bid) for moderate to severe chronic osteoarthritis and low back pain (11). Tapentadol PR is indicated in Europe for the management of severe chronic pain in adults, which can be adequately managed only with opioid analgesics, and in the United States (as tapentadol ER) for the management of moderate to severe chronic pain in adults and for the management of neuropathic pain associated with diabetic peripheral neuropathy in adults (As of April 2014, the indication in the United States has been reworded to accommodate class labeling for extended-release long-acting opioids; the current wording states the following: tapentadol is indicated for the management of pain and for the management of neuropathic pain associated with diabetic peripheral neuropathy in adults severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate) when a continuous, around-the-clock opioid analgesic is needed for an extended period of time. The current study evaluated the efficacy and tolerability of tapentadol PR (100 – 250 mg bid) for the management of moderate to severe chronic malignant tumor-related pain compared with placebo and morphine sulfate CR (40 – 100 mg bid).

Methods

This study was conducted in accordance with International Conference on Harmonisation Good Clinical Practice guidelines, the ethical principles of the Declaration of Helsinki, and applicable local laws. All patients signed an informed consent form prior to study participation. The protocol, amendments, and informed consent forms were approved by independent ethics committees at each site.

Patients

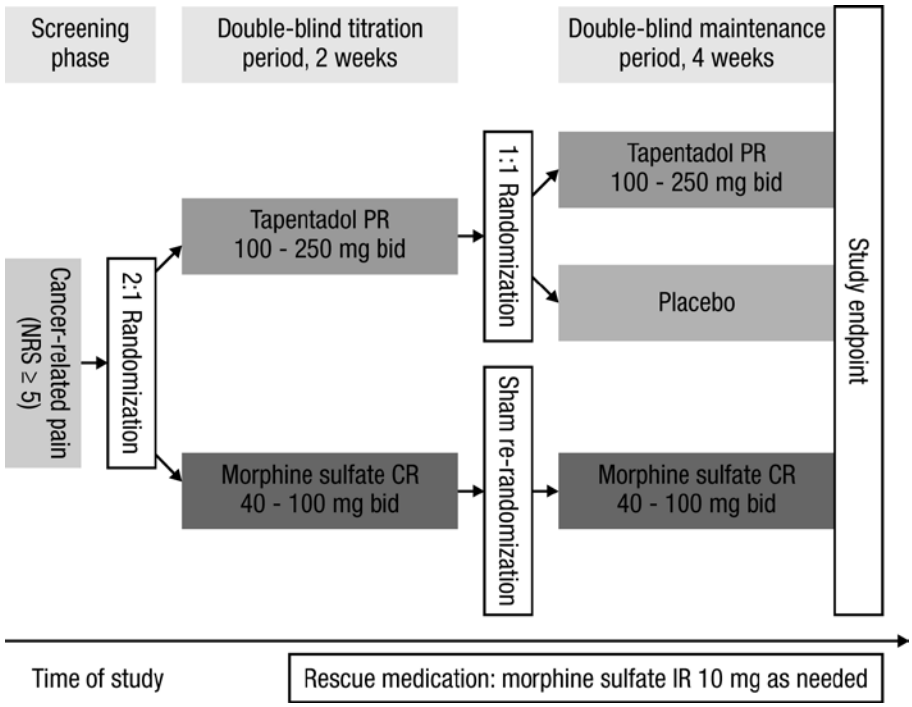
This study included men and women ≥ 18 years of age with chronic, malignant tumor-related pain. Patients were required to have a pain intensity score ≥ 5 on an 11-point numerical rating scale (NRS; 0 = "no pain" to 10 = "pain as bad as you can imagine") under their prior analgesic regimen at the start of titration. Patients must have been opioid naive or dissatisfied with their prior opioid treatment (dose equivalent of oral morphine ≤ 160 mg/day). Exclusion criteria are summarized in Table 1.

Radiotherapy and/or treatment by a pain-modifying chemotherapy protocol were prohibited within 30 days of screening and during the study. Patients were not permitted to take any analgesics other than the study drug or rescue medication during the study. Patients were also not permitted to take anti-Parkinsonian drugs, neuroleptics, serotonin noradrenaline reuptake inhibitors, and monoamine oxidase inhibitors within 14 days prior to screening and during the study. Adjuvant analgesics (e.g., antidepressants, anticonvulsants, muscle relaxants, corticosteroids, bisphosphonates, phytopharmaceutics), selective serotonin reuptake inhibitors, benzodiazepines, and acetylsalicylic acid (≤ 325 mg/day orally) for cardiovascular prophylaxis were permitted only if patients were taking a stable dose for ≥ 30 days prior to screening and during the study. Patients could continue receiving transcutaneous electrical nerve stimulation, acupuncture, and other similar interventional adjunctive therapies only if these procedures were administered at the same frequency with no change in routine for ≥ 30 days prior to screening and during the study.

Table 1. *Exclusion criteria*.

Received an experimental drug or used an experimental medical device within 30 days before the planned start of treatment
Concurrently participating in another study
Participated in a previous tapentadol study
History of alcohol and/or drug abuse
Life-long history of seizure disorder or epilepsy
Mild or moderate traumatic brain injury, stroke, or transient ischemic attack within one year
Severe traumatic brain injury within 15 years
History and/or presence of cerebral tumor or cerebral metastases
Chronic hepatitis B or C or active hepatitis B or C within 3 months
Human immunodeficiency virus infection
Moderately or severely impaired hepatic function
Alanine transaminase and/or aspartate transaminase levels > 3 times the upper limit of normal
Severely impaired renal function (creatinine clearance < 30 mL/min[a])
Hypercalcemia (corrected total serum calcium levels > 3.0 mmol/L)
Uncontrolled hypertension
Inadequate baseline bone marrow reserve (white blood cell count ≤ 3,500/μL, platelet count ≤ 100,000/μL, and hemoglobin level ≤ 9.5 g/dL)
Any scheduled surgery or any painful procedure during the study
Any clinically significant disease other than cancer that could affect efficacy or safety assessments

[a]Calculated from serum creatinine concentrations according to the method of Cockcroft and Gault (23).



PR, prolonged release; bid, twice daily; CR, controlled release; NRS, numerical rating scale; IR, immediate release.

Fig. 1. *Study design*.

Study Design

This multicenter, placebo- and active-controlled, double-blind, phase 3 study (ClinicalTrials.gov Identifier: NCT00472303) included a screening period lasting up to 7 days, a 2-week titration period, and a 4-week maintenance period (Fig. 1). This study design included both parallel-arm and randomized-withdrawal portions, each of which was used to test a different objective. The randomized-withdrawal portion of the study was used to evaluate the benefit of treatment with tapentadol PR (100 – 250 mg bid) compared with placebo during the maintenance period in an enriched population that had an initial response to and tolerated tapentadol PR treatment during the titration period. The parallel-arm portion of the study was used to determine whether the efficacy of tapentadol PR (100 – 250 mg bid) was non-inferior to that of morphine CR (40 – 100 mg bid), which has proven efficacy for the management of chronic, malignant tumor-related pain (3), during the titration period. A formal statistical comparison between morphine CR and tapentadol PR, or morphine CR and placebo, during the maintenance period, was limited to descriptive statistics because only patients who fulfilled the stabilization criteria (described below) were re-randomized to treatment during the maintenance period. This resulted in treatment groups during maintenance composed only of patients who had an initial response to and tolerated either tapentadol PR (placebo and tapentadol PR groups) or morphine CR (morphine CR group).

Randomization was based on computer-generated randomization lists, balanced using permuted blocks of treatments and stratified by center; randomization was implemented by a computer-based Interactive Voice Response System. The blind was not broken until all patients completed the trial and the database was locked, except in case of emergency. During the 2-week titration period, patients were titrated to the dose of tapentadol PR (100 – 250 mg bid) or morphine sulfate CR (40 – 100 mg bid) that provided an optimal balance of pain relief and tolerability. Morphine sulfate immediate release (IR; 10 mg) was allowed daily as rescue medication (with no maximum dose) during the titration and maintenance periods. At the start of the titration period, patients were randomized (2:1) to treatment with starting doses of tapentadol PR 100 mg bid or morphine sulfate CR 40 mg bid (the minimum therapeutic doses for this study). Doses could be increased in increments of tapentadol PR 50 mg bid or morphine CR 20 mg bid at a minimum of 3-day intervals (after receiving the same dose 6 consecutive times) to a maximum therapeutic dose of tapentadol PR 250 mg bid or morphine CR 100 mg bid. For patients who experienced intolerable side effects, the dose could be decreased to the previous level.

Patients who met the following stabilization criteria during the last 3 days of titration were eligible to enter the maintenance period: a mean pain intensity score < 5 (11-point NRS) and a mean consumption of ≤ 20 mg/day of morphine IR. Patients who did not meet these criteria were to be discontinued. During the maintenance period, patients who were taking morphine CR during titration continued on the same optimal dose of morphine CR after a sham re-randomization; patients who were taking tapentadol PR were re-randomized (1:1) to placebo or their optimal dose of tapentadol PR. Patients who were randomized to placebo received tapentadol PR 100 mg bid for 3 days to minimize withdrawal symptoms at the start of the maintenance period; from the fourth day of the maintenance period, these patients received placebo.

Study Evaluations

Patients recorded their current pain intensity on an 11-point NRS (0 = "no pain" to 10 = "pain as bad as you can imagine") twice daily throughout the study. The primary efficacy endpoint was the proportion of patients classified as responders at the end of the maintenance period. A responder for this period was defined as a patient who completed ≥ 28 days of the maintenance period, had a mean pain intensity score < 5 during the maintenance period, and had a mean total daily dose of ≤ 20 mg/day of rescue medication during the maintenance period. Although definitions of responders are generally based exclusively on an improvement in pain intensity (e.g., a ≥ 50% improvement in pain intensity) (14,15), the definition of a responder for both the titration period (described below) and the maintenance period in the current study also included a measure of rescue medication use and a measure of treatment adherence that inherently includes a measure of tolerability (completion of the treatment period). The permitted unlimited use of rescue medication in the current study could mask differences in pain intensity between treatments, which necessitated the inclusion of the additional criteria for responder analyses. Thus, although responder analyses served as the primary efficacy endpoint in this study, these analyses included a direct measure of efficacy (pain intensity), an indirect measure of efficacy (use of rescue medication), and a measure of tolerability and other reasons for discontinuing (completion of the treatment period).

Responder rates at the end of the titration period and the changes in mean pain intensity (11-point NRS) from the start of titration to each week of titration and from the start of the maintenance period to each week of the maintenance period were evaluated as secondary efficacy endpoints. For the end of the titration period, a responder was defined as a patient who completed the titration period and had a mean pain intensity score < 5 during the last 3 days of the titration period and a mean total daily dose of rescue medication ≤ 20 mg/day during the last 3 days of titration. Mean pain intensity at the start of the maintenance period was calculated as the mean of average daily pain intensity scores during the last 3 days of the titration period. Mean weekly pain intensity during the maintenance period was calculated as the mean of average daily pain intensity scores during each week of the maintenance period.

All AEs were coded using the *Medical Dictionary for Regulatory Activities* (MedDRA) Version 15.0. A treatment-emergent AE (TEAE) for each treatment period was defined as any AE that newly occurred or worsened after the first intake of the study drug during the respective treatment period.

Statistical Analyses

An estimated sample size of 108 patients per group for the tapentadol PR and placebo groups in the maintenance period was required to provide 80% power to detect a 20% difference in responder rates between the 2 groups at an $\alpha = 0.05$. Assuming a dropout rate of 35% during the titration period, an estimated 498 patients would need to be randomized to treatment during titration.

The safety population for the titration period included all randomized patients who received ≥ 1 dose of study drug during titration; the safety population for the maintenance period included all re-randomized patients who received ≥ 1 dose of study drug during maintenance. The respective full analysis (efficacy) populations included the same patients as the safety populations, except in cases of Good Clinical Practice compliance issues. The per-protocol populations were subsets of the full analysis populations that included patients with no major protocol violations that could potentially affect efficacy during the study.

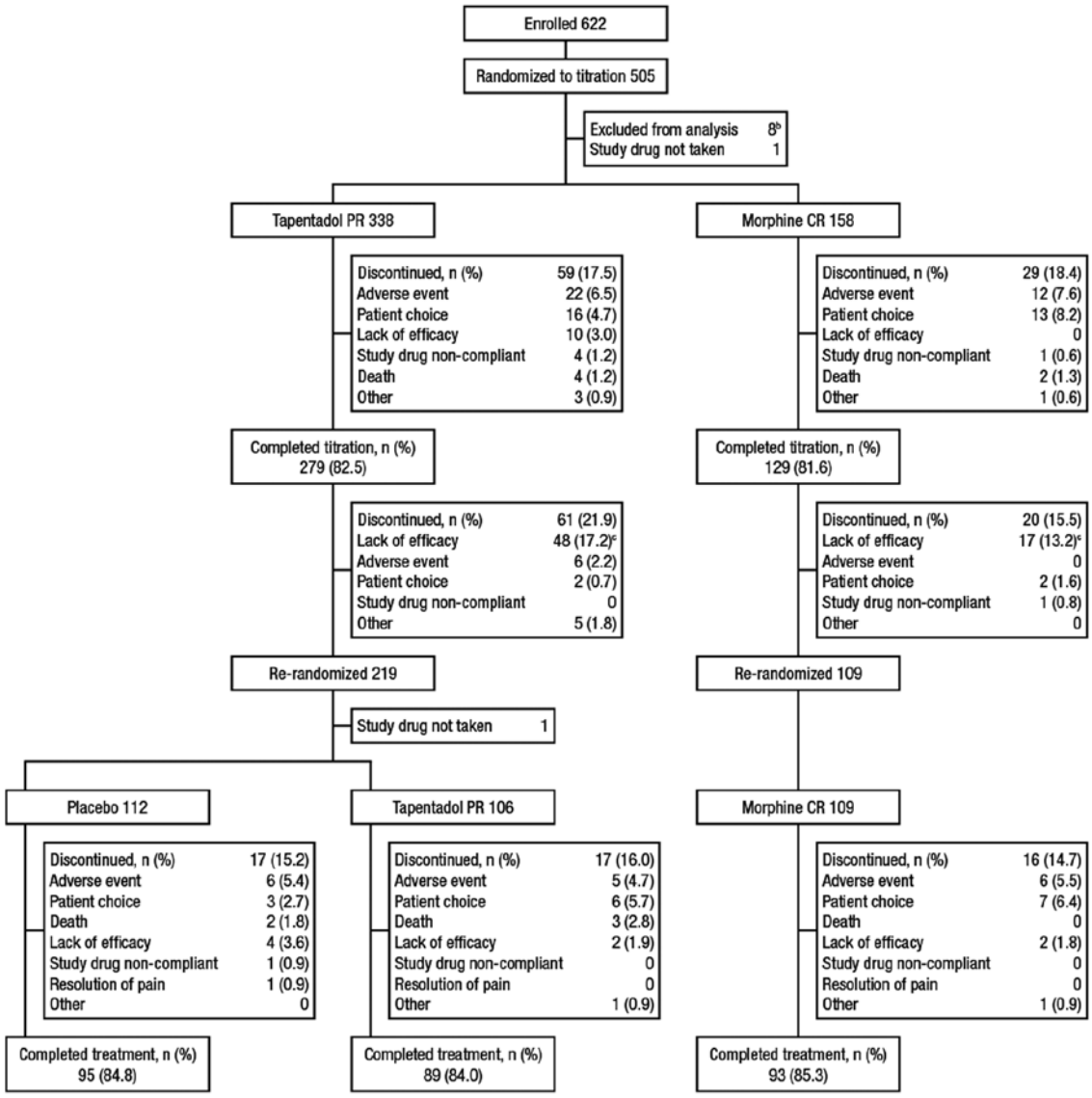
For the primary efficacy analysis, all intermittent missing pain intensity scores were imputed using linear interpolation; missing pain intensity scores following patient discontinuation during the titration or maintenance periods were imputed using the last observation carried forward (LOCF). Responder rates during the maintenance period were analyzed in the full analysis population using a logistic regression model, with treatment group and pooled center as factors and pain intensity at the start of maintenance as a covariate. As a sensitivity analysis, responder rates during the maintenance period were analyzed in the per-protocol population using a similar logistic regression model.

A Farrington-Manning non-inferiority test (16) was used to evaluate the non-inferiority of tapentadol PR compared with morphine CR based on responder rates at the end of the titration period (per-protocol population). The prespecified non-inferiority margin was 20%; non-inferiority would be concluded if the lower limit of the 95% confidence interval (CI) for the difference between the tapentadol PR responder rate minus the morphine CR rate was ≥ –20%. As a sensitivity analysis, the same non-inferiority comparison was performed in the full analysis population of the titration period. The selected non-inferiority margin was based on data obtained from a previous trial comparing tapentadol PR to placebo (ClinicalTrials.gov Identifier: NCT00505414). In that study, the difference in response rates between the tapentadol PR and placebo groups was 32%. Retaining at least 50% of this difference for a non-inferiority margin yields a margin of 16%; however, the margin was increased to 20% because the non-inferiority test for tapentadol PR to morphine CR was evaluated over the titration period when the response could be less stable than in the maintenance period. The responder rate during the maintenance period was also evaluated based on the presence of nociceptive, neuropathic, and visceral pain components at screening (based on the investigator's assessment).

Change in mean pain intensity (based on observed values) from the start to each week of the maintenance period was analyzed using a mixed model repeated measures (MMRM) analysis, including treatment, pooled center, week, and treatment-by-week interaction as factors, and pain intensity at the start of the maintenance period as a covariate. Between-group differences were estimated and tested with appropriate contrasts of the treatment and treatment-by-week effects.

As post hoc analyses, differences between the tapentadol PR and morphine CR treatment groups in the incidences of gastrointestinal disorders, general disorders and administration site conditions, nervous system disorders overall, and the following specific TEAEs (incidence ≥ 5% during the titration period) were evaluated during the titration period: constipa-

tion, dry mouth, nausea, vomiting, fatigue, dizziness, and somnolence. For patients who were re-randomized to receive treatment in the maintenance phase, differences between the tapentadol PR and morphine CR treatment groups in the overall incidence of gastrointestinal disorders during the titration and maintenance phases were evaluated. A logistic regression model with treatment as a factor was used to evaluate the differences in the incidences of these TEAEs. As described previously in Study Design, formal comparisons of results (including tolerability outcomes) between morphine CR and tapentadol PR or placebo during the maintenance period were limited to descriptive statistics.



PR, prolonged release; CR, controlled release, NRS, numerical rating scale. [a]Percentages for reasons for discontinuation during each of the study phases may not sum to the total discontinued during that phase due to rounding. [b]Eight patients at a single study site were excluded from efficacy and safety analyses due to Good Clinical Practice non-compliance. [c]Patients who did not meet the stabilization criteria (mean pain intensity < 5 points/day [11-point NRS] and mean total daily dose of rescue medication ≤ 20 mg during the last 3 days of the titration period) were not re-randomized to treatment during the maintenance period.

Fig. 2. *Patient disposition*.[a]

Results

Patients and Treatment Exposure

This study was conducted from June 13, 2007, to June 4, 2012. Overall, 622 patients were enrolled at 71 sites in 16 countries. The flow of patients through the study is summarized in Fig. 2. Eight patients at a single study site were excluded from all efficacy and safety analyses due to Good Clinical Practice non-compliance. The safety population for the titration period included 496 patients, and the full analysis (efficacy) population for the titration period included 492 patients (4 from the safety population were excluded from the full analysis population because their e-diaries were inappropriately accessed by another person). For the maintenance period, the safety population included 327 patients and the full analysis (efficacy) population included 325 patients (2 from the safety population were excluded from the full analysis population for the above-listed reason).

During the titration period, 17.5% (59/338) of patients in the tapentadol PR group and 18.4% (29/158) of patients in the morphine CR group discontinued treatment. In the tapentadol PR and morphine CR groups, respectively, a total of 21.9% (61/279) and 15.5% (20/129) of patients who completed titration did not enter the maintenance period. Of those who completed titration but did not enter the maintenance period, 78.7% (48/61) of patients in the tapentadol PR group and 85.0% (17/20) of patients in the morphine CR group did not enter the maintenance period because they failed to meet the response criteria. During the maintenance period, 15.2% (17/112) of patients in the placebo group, 16.0% (17/106) of patients in the tapentadol PR group, and 14.7% (16/109) of patients in the morphine CR group discontinued treatment. Reasons for treatment discontinuation are summarized in Fig. 2.

Baseline and demographic characteristics (including percentages of patients who had previously taken opioid analgesics and mean [standard deviation (SD)] pain intensity scores at the start of titration and maintenance) for the maintenance period safety population are summarized in Table 2.

The most commonly reported tumor diagnoses (incidence ≥ 5%) at baseline in the maintenance safety population are summarized in Table 2. In the maintenance safety population, metastases were present in 81.3% (91/112) of patients in the placebo group, 83.0% (88/106) of patients in the tapentadol PR group, and 78.9% (86/109) of patients in the morphine CR group. Bone metastases were present in 30.4% (34/112) of patients in the placebo group, 35.8% (38/106) of patients in the tapentadol PR group, and 31.2% (34/109) of patients in the morphine CR group, and spine metastases were present in 17.0% (19/112), 11.3% (12/106), and 9.2% (10/109) of patients in the placebo, tapentadol PR, and morphine CR groups, respectively. Lung metastases were present in a higher percentage of patients in the tapentadol PR group (21.7% [23/106]) than in the placebo group (15.2% [17/112]) or morphine CR group (16.5% [18/109]), as were liver metastases (placebo, 14.3% [16/112]; tapentadol PR, 18.9% [20/106]; morphine CR, 16.5% [18/109]).

During both the titration and maintenance periods, the median modal (i.e., most frequently used) daily dose for tapentadol PR was 300.0 mg and for morphine sulfate CR was 120.0 mg. The median duration of treatment was 14 days for the tapentadol PR and morphine CR treatment groups during the titration period, and 28 days for the placebo, tapentadol PR, and morphine CR treatment groups during the maintenance period.

Efficacy

For the primary efficacy endpoint, the adjusted estimates of the responder rates from the logistic regression model (controlling for differences in the pain intensity at the start of the maintenance period and differences across pooled treatment centers) are summarized in Fig. 3; the odds of being a responder in the tapentadol PR group were approximately twice the odds of being a responder in the placebo group ($P = 0.020$; Fig. 3). The observed responder rates during the maintenance period in the placebo, tapentadol PR, and morphine CR groups, respectively, were 49.5% (55/111), 61.9% (65/105), and 68.8% (75/109). Patients who were non-responders only because they used > 20 mg/day of rescue medication during the maintenance period (placebo 25.2% [28/111]; tapentadol PR, 14.3% [15/105]; morphine CR, 12.8% [14/109]) accounted for most of the overall difference in responder rates between the tapentadol PR and placebo groups. Observed responder rates during the maintenance period for patients with nociceptive, neuropathic, and visceral pain components are summarized in Table 3. Numerically greater responder rates were observed for tapentadol PR than for placebo regardless of the type of pain.

Responder rates at the end of the titration period in the tapentadol PR and morphine CR groups, respectively, are summarized in Fig. 4 for the per protocol population. As the lower limit of the 2-sided 95% CI

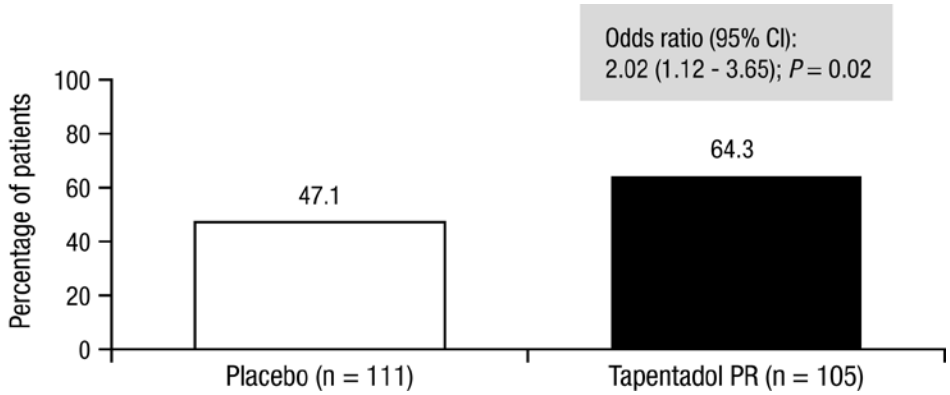
Table 2. *Baseline and demographic characteristics and cancer-related medical history (maintenance safety population).*

Characteristic	Placebo (n = 112)	Tapentadol PR (n = 106)	Morphine CR (n = 109)
Age, y			
Mean (SD)	60.8 (11.1)	59.3 (10.0)	60.6 (10.4)
Age category, n (%)			
< 65 y	75 (67.0)	71 (67.0)	76 (69.7)
≥ 65 y	37 (33.0)	35 (33.0)	33 (30.3)
Gender, n (%)			
Male	56 (50.0)	59 (55.7)	59 (54.1)
Female	56 (50.0)	47 (44.3)	50 (45.9)
Race, n (%)			
White	112 (100.0)	106 (100.0)	109 (100.0)
Body mass index, kg/m^2			
Mean (SD)	25.2 (5.55)	25.2 (5.42)	25.7 (5.42)
Opioid pretreatment, n (%)	95 (84.8)	91 (85.8)	92 (84.4)
Nociceptive pain, n (%)	81 (72.3)	73 (68.9)	84 (77.1)
Neuropathic pain, n (%)	76 (67.9)	68 (64.2)	71 (65.1)
Visceral pain, n (%)	51 (45.5)	54 (50.9)	55 (50.5)
Start-of-titration pain intensity[a]			
Mean (SD)	6.14 (1.45)	6.28 (1.45)	5.99 (1.52)
Start-of-maintenance pain intensity[a]			
Mean (SD)	2.88 (1.19)	3.14 (1.16)	2.83 (1.39)
Primary tumor diagnosis at baseline,[b] n (%)			
Malignant breast and nipple neoplasms	16 (14.3)	19 (17.9)	17 (15.6)
Malignant non-small cell neoplasms of the respiratory tract, cell type unspecified	10 (8.9)	17 (16.0)	17 (15.6)
Malignant prostatic neoplasms	17 (15.2)	15 (14.2)	11 (10.1)
Malignant respiratory tract and pleural neoplasms, cell type unspecified NEC	15 (13.4)	15 (14.2)	8 (7.3)
Malignant colonic neoplasms	3 (2.7)	8 (7.5)	6 (5.5)
Malignant renal neoplasms	3 (2.7)	4 (3.8)	7 (6.4)
Malignant rectal neoplasms	4 (3.6)	4 (3.8)	6 (5.5)
Malignant cervix neoplasms	6 (5.4)	1 (1.9)	3 (2.8)
Malignant pancreatic neoplasms (excluding islet cell and carcinoid)	3 (2.7)	1 (0.9)	6 (5.5)

PR, prolonged release; CR, controlled release; SD, standard deviation; NRS, numerical rating scale; NEC, not elsewhere classified.
[a]Pain intensity was rated on an 11-point NRS.
[b]Includes only the most commonly reported high-level terms for tumor diagnoses (reported for ≥ 5% of patients in any treatment group).

for the between-group difference was –15.5%, tapentadol PR was found to be non-inferior to morphine CR. Consistent results for the non-inferiority of tapentadol PR to morphine CR were observed in the full analysis population (responder rates: tapentadol PR, 63.9% [214/335]; morphine CR, 68.2% [107/157]; lower limit of the 95% CI for the between-group difference in responder rates, –12.7%; $P < 0.001$). Non-inferiority for tapentadol PR versus morphine CR during the titration period was established at a dose ratio of 2.5:1 based on the median modal daily doses (Fig. 4).

In the full analysis population for the titration period, mean pain intensity scores in the tapentadol PR and morphine CR group improved by > 2 points from the start to the end of the titration period; mean (SD) pain intensity scores were 6.34 (1.46) and 6.26 (1.56),



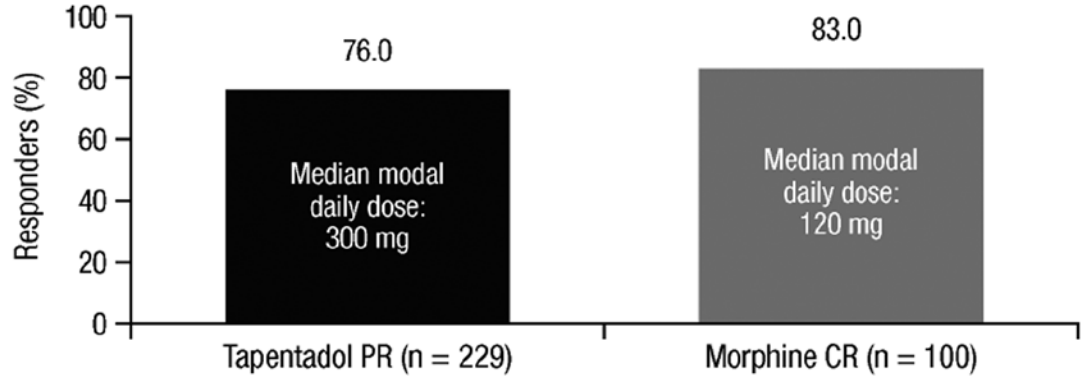
PR, prolonged release; CI, confidence interval; NRS, numerical rating scale. [a]Analyzed using a logistic regression model, with treatment group and pooled center as factors, and current pain intensity at the start of the maintenance period as a covariate. [b]A responder was defined as a patient who completed ≥ 28 days of maintenance, had a mean pain intensity score < 5 (11-point NRS) during maintenance, and used ≤ 20 mg/day of rescue medication on average during maintenance.

Fig. 3. *Adjusted estimates of responder rates during the maintenance period in the placebo and tapentadol PR groups [a,b].*

Table 3. *Responder rates during the maintenance period based on the presence of nociceptive, neuropathic, or visceral pain components at screening (maintenance full analysis population).*

	Placebo (n = 111)		Tapentadol PR (n = 105)		Morphine CR (n = 109)	
Pain component present at screening	**n**	**Responder rate, n (%)**	**n**	**Responder rate, n (%)**	**n**	**Responder rate, n (%)**
Nociceptive pain component	80	35 (43.8)	72	46 (63.9)	84	59 (70.2)
Neuropathic pain component	76	41 (53.9)	68	50 (73.5)	71	48 (67.6)
Visceral pain component	50	19 (38.0)	53	27 (50.9)	55	30 (54.5)

PR, prolonged release; CR, controlled release.



PR, prolonged release; CR, controlled release; NRS, numerical rating scale. [a]A responder at the end of the titration period was defined as a patient who completed titration, had a mean pain intensity score < 5 (11-point NRS) during the last 3 days of titration, and used ≤ 20 mg/day of rescue medication on average during the last 3 days of titration.

Fig. 4. *Observed responder rates and median modal daily doses at the end of the titration period (per-protocol population) [a].*

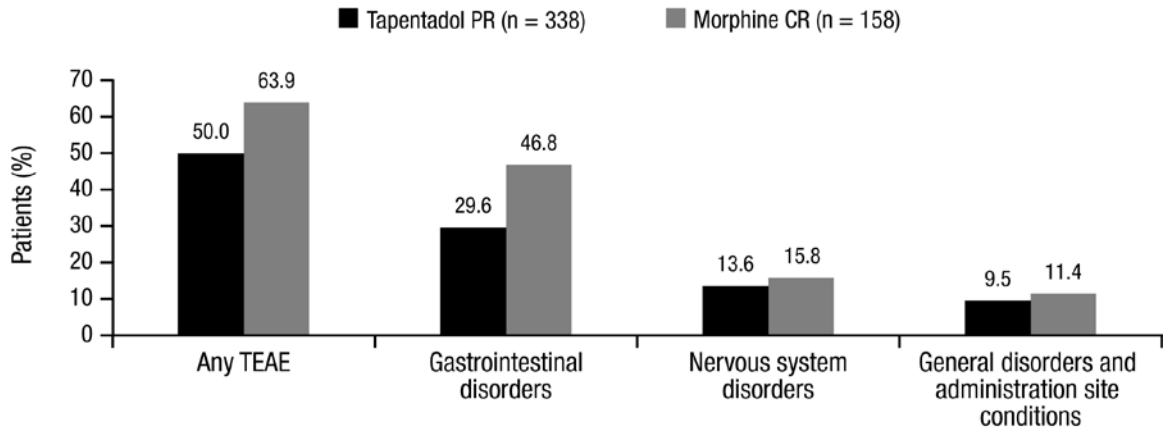
respectively, at the start of titration, and 4.05 (1.80) and 3.69 (1.84), respectively, at Week 2 of titration. In the full analysis population for the maintenance period, mean (SD) pain intensity scores at the start of titration in the placebo group (received tapentadol PR during titration), tapentadol PR group (received tapentadol PR during titration), and morphine CR group (received morphine CR during titration), respectively, were 6.15 (1.45), 6.26 (1.44), and 5.99 (1.52). Reductions in mean pain intensity of > 3 points were observed in all 3 maintenance treatment groups over the course of the titration period with tapentadol PR or morphine CR treatment (mean [standard error] change in pain intensity from the start of titration to the start of the maintenance period: placebo, –3.29 [0.16]; tapentadol PR, –3.09 [0.17]; morphine CR, –3.09 [0.19]). Improvements in pain intensity achieved during the titration period were sustained during the maintenance period in all 3 maintenance treatment groups. However, there were no statistically significant differences observed between the tapentadol PR and placebo groups for the change in pain intensity from the start of the maintenance period to Weeks 1, 2, 3, or 4 of the maintenance period ($P \geq 0.152$).

During the titration period, 71.9% (241/335) of patients in the tapentadol PR group and 58.0% (91/157) of patients in the morphine CR group took rescue medication (morphine IR). The mean (SD) total daily doses of rescue medication used during the titration period were 13.31 (17.41) mg in the tapentadol PR group and 8.87 (12.50) mg in the morphine CR group. During the maintenance period, 72.1% (80/111) of patients in the placebo group, 71.4% (75/105) in the tapentadol PR group, and 61.5% (67/109) in the morphine CR group took rescue medication. In the placebo, tapentadol PR, and morphine CR groups, respectively, the mean (SD) total daily doses of rescue medication used during the maintenance period were 13.65 (13.67) mg, 11.20 (12.74) mg, and 8.91 (14.95) mg. As described above, more patients in the placebo group used ≥ 20 mg/day of morphine IR compared with the tapentadol PR or morphine CR groups.

Safety and Tolerability

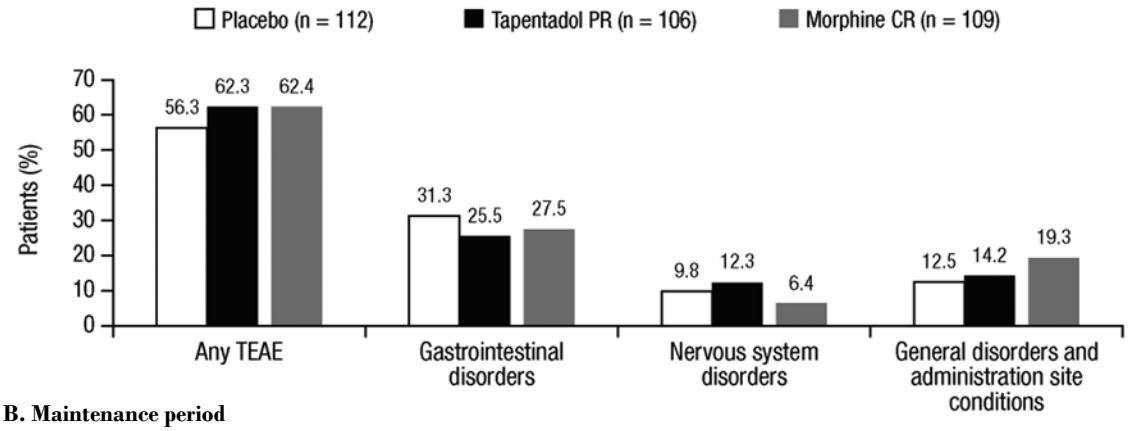
During the titration period, 50.0% (169/338) of patients in the tapentadol PR group and 63.9% (101/158) of patients in the morphine CR group reported ≥ 1 TEAE. During the maintenance period, 56.3% (63/112) of patients in the placebo group, 62.3% (66/106) of patients in the tapentadol PR group, and 62.4% (68/109) of patients in the morphine CR group reported ≥ 1 newly emerging TEAE (i.e., a TEAE that started or worsened after the titration period). The overall TEAE incidence and the overall incidences of gastrointestinal disorders, nervous system disorders, and general disorders and administration site conditions during the titration and maintenance period are summarized in Fig. 5. Selected TEAEs with an incidence ≥ 5% in any treatment group during the titration period or maintenance period are summarized in Fig. 6. Based on post hoc analyses, the incidences of TEAEs overall and gastrointestinal disorders overall and the incidences of nausea, vomiting, and dry mouth were significantly lower in the tapentadol PR group than in the morphine CR group during the titration period ($P \leq 0.0039$ for all comparisons; Figs. 5 and 6). No additional TEAEs to those shown in Fig. 6 were reported by ≥ 5% of the patients in either treatment group during the titration period. During the maintenance period, the following additional TEAEs were reported by ≥ 5% of patients in any treatment group: malignant neoplasm (placebo, 3.6% [4/112]; tapentadol PR, 8.5% [9/106]; morphine CR, 3.7% [4/109]), decreased appetite (placebo, 5.4% [6/112]; tapentadol PR, 7.5% [8/106]; morphine CR, 5.5% [6/109]), and hyperhidrosis (placebo, 0.9% [1/112]; tapentadol PR, 3.8% [4/106]; morphine CR, 6.4% [7/109]). For patients who were re-randomized to the maintenance phase, TEAEs with an incidence > 10% during the titration and maintenance phases are provided in Appendix 1. The overall incidence of gastrointestinal TEAEs for these patients during the 2 phases combined was 39.6% in the tapentadol group and 55.0% in the morphine group (OR, 1.866 [95% CI, 1.085 – 3.209]).

The incidence of TEAEs leading to discontinuation was low during the titration period (tapentadol PR, 8.6% [29/338]; morphine CR, 7.0% [11/158]) and during the maintenance period (placebo, 4.5% [5/112]; tapentadol PR, 4.7% [5/106]; morphine CR, 6.4% [7/109]). In the tapentadol PR and morphine CR groups, respectively, serious TEAEs were reported by 7.4% (25/338) and 3.8% (6/158) of patients during the titration period; the most common system organ class of serious TEAEs (≥ 2%) during titration was neoplasms, benign, malignant, and unspecified (2.1% [7/338] vs 1.3% [2/158]). In the placebo, tapentadol PR, and morphine CR groups, respectively, 8.9% (10/112), 11.3% (12/106), and 5.5% (6/109) of patients experienced serious TEAEs during the maintenance period; the most common system organ classes of serious TEAEs (≥ 2%) during maintenance were neoplasms, benign, malignant, and unspecified



Odds ratio for morphine CR vs tapentadol PR	1.772	2.097	1.193	1.229
95% CI	1.202 - 2.613	1.419 - 3.097	0.703 - 2.024	0.667 - 2.265
P value	0.0039	0.0002	0.5123	0.5076

A. Titration period



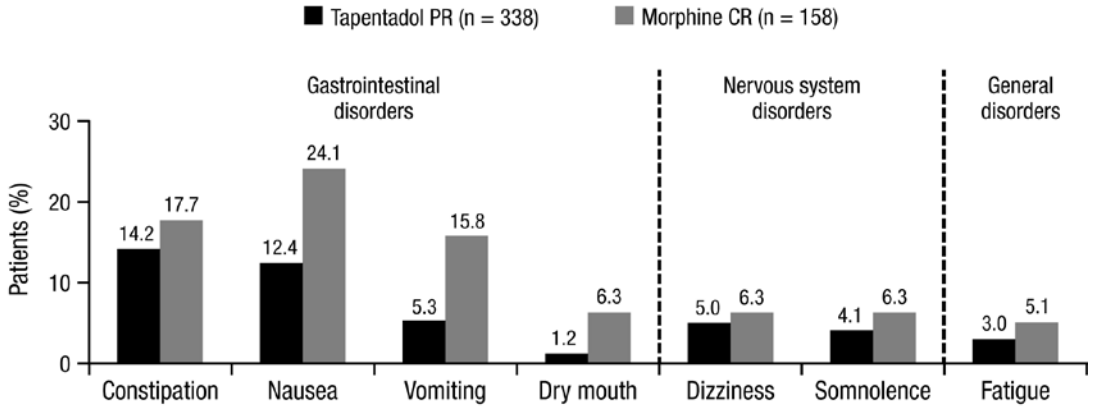
B. Maintenance period

TEAE, treatment-emergent adverse event; PR, prolonged release; CR, controlled release; CI, confidence interval.
[a]Incidence based on the number of patients experiencing ≥ 1 TEAE, not the number of TEAEs.
[b]A formal comparison between morphine CR and tapentadol PR or placebo during the maintenance period was limited to descriptive statistics, as described in the Methods.

Fig. 5. Overall TEAE incidence and incidence of gastrointestinal disorders, nervous system disorders, and general disorders and administration site conditions during the A) titration period, and B) maintenance period (safety populations) [a].

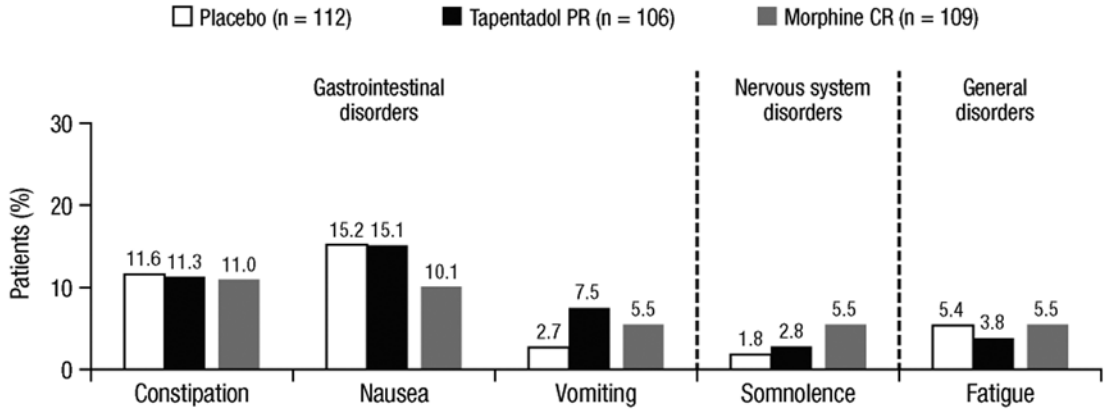
(placebo, 1.8% [2/112]; tapentadol PR, 4.7% [5/106]; morphine CR, 0.9% [1/109]) and general disorders and administration site conditions (placebo, 0%; tapentadol PR, 2.8% [3/106]; morphine CR, 0%). The serious TEAEs in the general disorders and administration site conditions system organ class that were reported in the tapentadol PR group were death (n = 2), which will be discussed in further detail later in this section, and general physical health deterioration (n = 1).

During the titration period (including up to 30 days after the last dose for patients who dropped out in the titration period), 3.6% (12/338) of patients in the tapentadol PR group and 1.9% (3/158) of patients in the morphine CR group experienced TEAEs leading



	Constipation	Nausea	Vomiting	Dry mouth	Dizziness	Somnolence	Fatigue
Odds ratio for morphine vs tapentadol PR	1.301	2.232	3.342	5.642	1.276	1.564	1.749
95% CI	0.782 - 2.167	1.371 - 3.633	1.764 - 6.330	1.741 - 18.280	0.570 - 2.854	0.679 - 3.602	0.677 - 4.521
P value	0.3114	0.0012	0.0002	0.0039	0.5530	0.2937	0.2484

A. Titration period



B. Maintenance period

TEAE, treatment-emergent adverse event; PR, prolonged release; CR, controlled release; CI, confidence interval.
[a]Incidence based on the number of patients experiencing ≥ 1 TEAE, not the number of TEAEs.
[b]A formal comparison between morphine CR and tapentadol PR or placebo during the maintenance period was limited to descriptive statistics, as described in the Methods.

Fig. 6. *Selected TEAEs reported by ≥ 5% of patients during the A) titration period, or B) maintenance period (safety populations)* [a,b].

to death; these TEAEs were counted for the titration period irrespective of the time point of death. During the maintenance period (including up to 30 days after the last dose), 1.8% (2/112) of patients in the placebo group, 6.6% (7/106) of patients in the tapentadol PR group, and no patients in the morphine CR group experienced TEAEs leading to death. In the majority of deaths (57.9% [11/19]) among patients treated with tapentadol PR, the TEAE with a fatal outcome was a malignant neoplasm or was another TEAE that was considered related to malignant neoplasm or was accompanied by an additional TEAE of malignant neoplasm. Consistent with the nature of the underlying disease of cancer, all TEAEs with a fatal outcome were considered

by the investigators to be unrelated or unlikely related to study treatment. Overall, the nature of TEAEs with a fatal outcome did not suggest a common pattern or a causal relationship with tapentadol PR.

The most common primary tumor for the patients treated with tapentadol PR who experienced a TEAE with a fatal outcome was lung cancer (36.8% [7/19]). All but one of the patients treated with tapentadol PR who experienced a TEAE with a fatal outcome had metastases (94.7% [18/19]); 84.2% (16/19) of these patients had distant metastases and 36.8% (7/19) had lymph node involvement. Of the patients treated with tapentadol PR who experienced a TEAE with a fatal outcome, 36.8% (7/19) had liver metastases and 21.1% (4/19) had lung metastases. As described above, the incidences of lung and liver metastases at screening were higher in the tapentadol PR group than in the placebo or morphine CR groups of the maintenance safety population. The one tapentadol PR–treated patient who experienced a TEAE with a fatal outcome, and did not have metastases, had a cancer relapse.

Discussion

Results of the current large-scale study showed that tapentadol PR (100 – 250 mg bid) was effective compared with placebo based on the primary endpoint (response rate during the maintenance period) for the management of moderate to severe, chronic, malignant tumor-related pain. For the primary endpoint, the odds of being a responder in the tapentadol PR group were twice the odds of being a responder in the placebo group. In the current study, the definition of a responder for the primary endpoint was based on pain intensity, duration of treatment, and rescue medication use criteria. The pain intensity criterion was included based on the recommended use of pain intensity ratings as a core outcome measure of chronic pain studies (14). Rescue medication use was considered in the definition of a responder because patients were permitted to take unlimited amounts of rescue medication, and the individual amount of rescue medication used could have contributed to patient response to treatment. Differences in rescue medication use were identified as the main factor involved in differences in response rates for tapentadol PR and placebo during the maintenance period. Daily rescue medication use of morphine sulfate IR 20 mg is a reasonable upper limit for the definition of a responder because (based on cancer pain guidelines) doses for breakthrough pain should be equivalent to 10% to 15% of the daily opioid dose (17).

Based on responder rates during the 2-week titration period, the analgesic efficacy of tapentadol PR (100 – 250 mg bid) was non-inferior to that of morphine sulfate CR (40 – 100 mg bid). Comparisons of the efficacy of tapentadol PR to that of morphine CR were performed only for the titration period, not for the maintenance period, because patients who had an initial response to and tolerated tapentadol PR during titration were assigned to the tapentadol PR and placebo groups during maintenance, and patients who had an initial response to and tolerated morphine CR during titration were assigned to the morphine CR group; the enrichment of both the tapentadol PR and morphine CR groups could potentially affect comparisons of efficacy during the maintenance period. Responder rates during the maintenance period were also numerically greater for tapentadol PR than for placebo in patients with nociceptive, neuropathic, and visceral components to their pain.

Tapentadol PR treatment was associated with better overall tolerability and gastrointestinal tolerability than morphine CR treatment during the titration period (i.e., lower incidences of TEAEs overall; gastrointestinal TEAEs overall; and individual TEAEs of nausea, vomiting, and dry mouth). In addition, the odds of experiencing a gastrointestinal TEAE during the titration and maintenance phases for those patients who entered the maintenance phase was nearly double for patients who received morphine CR compared with patients who received tapentadol PR. The ratio of median modal doses (i.e., most frequently taken doses) for tapentadol PR to morphine CR during the titration period was consistent with previously observed equipotency ratios (18).

Based on mean weekly pain intensity scores over the course of the study, clinically important improvements (change of > 2 on an 11-point NRS [19,20]) were observed for patients in the tapentadol PR and morphine CR treatment groups during the titration period. These improvements in pain intensity were maintained in the placebo, tapentadol PR, and morphine CR treatment groups over the course of the maintenance period. For the placebo group, no rapid increase in pain intensity was observed. This may have been related in part to the unlimited use of rescue medication (morphine IR) permitted throughout the treatment period and in part to the high placebo effect expected for chronic pain studies (21). Due to the permitted use of unlimited amounts of rescue medication, clear differences in pain intensity were not expected. The progressive nature of cancer may have resulted in increased difficulty in

establishing differences in secondary endpoints, such as pain intensity over time.

Tapentadol PR was generally well tolerated, with a low incidence of TEAEs leading to discontinuation and a low incidence of serious TEAEs during both the titration and maintenance periods. The higher rate of TEAEs with fatal outcomes in the tapentadol PR group was assessed as likely due to the more advanced disease state of patients in the tapentadol PR group relative to the other 2 treatment groups. In the tapentadol PR group, the incidence of TEAEs of malignant neoplasms was higher than in the other 2 treatment groups. In addition, the percentage of patients with liver and lung metastases at screening was higher in the tapentadol PR group than in the placebo or morphine CR groups. In general, patients in the tapentadol PR group with a TEAE with a fatal outcome were suffering from cancer with a poor prognosis (e.g., lung cancer).

The amount of rescue medication that patients were using may have been influenced not only by their requirement for additional analgesia, but also by the tolerability of their assigned study drug. The incidence of TEAEs, particularly gastrointestinal TEAEs, was higher in the morphine CR group than in the tapentadol PR group. Patients in the morphine CR group who were already experiencing AEs may have been less willing to take additional opioid analgesics (morphine IR) as rescue medication, resulting in an inverse correlation between the number of AEs in the morphine CR group and the intake of rescue medication. Therefore, the difference in the number of patients taking rescue medication during the titration period between the tapentadol PR and morphine CR groups may, in part, reflect a difference in tolerability rather than a difference in the need for rescue medication (i.e., a difference in efficacy).

A limitation of the present study is that the non-inferiority comparison of the efficacy of tapentadol PR (100 – 250 mg bid) with that of morphine sulfate CR (40 – 100 mg bid) was limited to the 2-week titration period due to the randomized-withdrawal design of the maintenance period. Patients in the maintenance period had been selected to continue treatment based on their response to and tolerance of study treatment during the titration period; the limitations of enrichment-based study designs have been described previously (22). Despite these limitations, this type of study is useful because it reflects patients' progression from initial treatment and titration to a stable dose (and the subsequent choice of whether to continue with chronic treatment) used in clinical practice. In addition, patients in the placebo group could not be considered to be exclusively placebo-treated because of the use of unlimited doses of rescue medication (morphine IR) throughout the study; however, the unlimited use of rescue medication was essential for the ethical conduct of this study to ensure that all patients with chronic malignant tumor-related pain achieved adequate analgesia.

Evidence of efficacy in cancer pain from placebo-controlled trials is generally lacking for the strong opioid analgesics used for the management of these patients (5). To our knowledge, this is the largest randomized, double-blind, placebo- and active-controlled clinical trial of an analgesic for cancer pain and, as such, this study adds substantially to the currently available information on cancer pain management.

Conclusions

Taken together, results of this study show that tapentadol PR (100 – 250 mg bid) is effective for the management of moderate to severe chronic malignant tumor-related pain and provides efficacy that is non-inferior to that of morphine CR (40 – 100 mg bid), but with an improved gastrointestinal tolerability profile.

Conflict of interest

H. G. Kress has received support for consultancy services from Astellas, Bial, Grunenthal GmbH, Linde Group, Mundipharma International Ltd., Teva/Cephalon, Philips, IBSA Foundation, and Bionorica Ethics Austria. D. Koch, H. Kosturski, C. Dogan, M. Eerdekens, and B. Lange are employees of Grünenthal GmbH. A. Steup was an employee of Grünenthal GmbH at the time this work was conducted. K. Karcher and M. Etropolski are employees of Janssen Research & Development, LLC, and Johnson & Johnson stockholders.

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