Accepted Manuscript

Safety and Efficacy of Once-Daily Hydromorphone Extended-Release Versus Twice-Daily Oxycodone HCl Controlled-Release in Chinese Patients with Cancer Pain: A Phase 3, Randomized, Double-Blind, Multi-Center Study

Shiying Yu , Wei Shen , Lu Yu , Yanyan Hou , John Han , Henry M. Richards

PII: S1526-5900(14)00720-2

DOI: 10.1016/j.jpain.2014.04.008

Reference: YJPAI 2935

To appear in: *Journal of Pain*

Received Date: 29 August 2013

Revised Date: 11 April 2014

Accepted Date: 29 April 2014

Please cite this article as: Yu S, Shen W, Yu L, Hou Y, Han J, Richards HM, Safety and Efficacy of Once-Daily Hydromorphone Extended-Release Versus Twice-Daily Oxycodone HCl Controlled-Release in Chinese Patients with Cancer Pain: A Phase 3, Randomized, Double-Blind, Multi-Center Study, *Journal of Pain* (2014), doi: 10.1016/j.jpain.2014.04.008.

Title

Safety and Efficacy of Once-Daily Hydromorphone Extended-Release Versus Twice-Daily Oxycodone HCl Controlled-Release in Chinese Patients with Cancer Pain: A Phase 3, Randomized, Double-Blind, Multi-Center Study

Authors: Shiying Yu[1], Wei Shen[2*], Lu Yu [3], Yanyan Hou[3], John Han[4], Henry M. Richards[4]

[1]Tongji Hospital affiliated to Tongji Medical College Huazhong University of Science & Technology, Wuhan, Hubei Province, China
[2]Xin Hua Hospital, Affiliated to Shanghai Jiao Tong University School of Medicine
[3]Xian-Janssen Pharmaceutical Company, Beijing, China
[4]Janssen Research & Development, LLC., New Jersey, USA

Running title: Hydromorphone Extended-Release for Cancer Pain

Words for indexing: brief pain inventory, cancer pain, hydromorphone extended-release, oxycodone, strong opioids

***Corresponding author**:

Dr. Lu Yu
Xi'an Janssen Pharmaceutical Ltd.
14F, Tower 3, China Central Place
No. 77 Jian Guo Road
Chao Yang District
Beijing, China 100025
Tel: +86-10-58218349/ +86-18601352026
Fax: +86-10-58218703
Email: lyu13@its.jnj.com

Abstract

Noninferiority of once-daily hydromorphone hydrochloride (HCl) extended-release's (hydromorphone ER) efficacy to twice-daily oxycodone HCl controlled-release (oxycodone CR) was investigated in this, randomized, double-blind study in Chinese patients with moderate to severe cancer pain requiring strong oral opioid analgesics. Randomization (1:1) to hydromorphone ER (8-32 mg) or oxycodone CR (10-40 mg) was followed by dose-titration (up to 8 days), and dose-maintenance (28-days, weekly visits). Primary endpoint was change from baseline to end of study in 'worst pain in the past 24 hours' of Brief Pain Inventory (short form) score on last observation carried forward (per protocol set [PPS]). 137/260 randomized patients completed maintenance phase (hydromorphone ER: n=70; oxycodone CR: n=67); PPS: 81 patients. Mean age was 53.1 years (range 18-70 years; males=65.3%); most common Eastern Cooperative Oncology Group performance status=2. LS mean difference between 2 treatment groups for primary endpoint using ANCOVA (baseline score, covariate) was −0.1 (95% confidence interval [CI]: −1.3, 1.1), with upper-bound of 95% CI <1.5 (predefined noninferiority margin). Most common reason for deaths was disease progression (hydromorphone ER: 6.3%; oxycodone CR: 12.7%). Treatment-emergent adverse events were comparable between treatment groups. Hydromorphone ER was noninferior to oxycodone CR in alleviating cancer pain and was well tolerated.

Trial registration No.: ClinicalTrials.gov: NCT01205126

Perspective

This article demonstrates clinical noninferiority of efficacy of once-daily hydromorphone extended-release compared with twice-daily oxycodone controlled-release in alleviating cancer

pain in Chinese patients, with comparable safety profiles between the two treatment groups. Thus, a treatment option with the potential for a reduced dosing frequency exists for healthcare providers and patients.

Keywords: brief pain inventory, cancer pain, hydromorphone extended-release, oxycodone, strong opioids

Introduction

Chronic moderate to severe pain is an inevitable symptom associated with advanced stages of cancer, hence alleviation of cancer pain is attributed prime importance in the WHO palliative care definition.[18] Morphine is the most commonly used strong opioid analgesic in the treatment of moderate to severe cancer pain. However other strong opioids such as hydromorphone and oxycodone can be used as alternatives.[3,21] Hydromorphone is a hydrogenated semisynthetic ketone of morphine that exerts its analgesic effects through μ-opioid receptors in the central nervous system (CNS).[19] Per-milligram, orally administered hydromorphone is approximately 5 times more potent than orally administered morphine.[15,22] Being a pure μ opioid agonist, hydromorphone has no ceiling effect and its maximum dose is based on the balance between efficacy and tolerability. For optimal pain control, opioids are to be administered 'by-the-clock' and not 'on demand' or 'as needed'.[3,16] However, frequent dosing is required for some opioid formulations, which may lead to poor adherence to therapy and thus result in inadequate analgesia and diminished quality of life.[4,9]

A once-daily extended-release hydromorphone hydrochloride (HCl) formulation has been developed using OROS® (Oral osmotic therapeutic system) Push-Pull™ osmotic active technology (ALZA Corporation, Mountain View, CA, USA) (hydromorphone ER).[8] This formulation is designed to release hydromorphone at a controlled rate for up to 24 hours for once-daily dosing and minimizes peak-trough plasma concentration fluctuations that are associated with the use of conventional immediate release (IR) formulations.[8] Therapy can be initiated with hydromorphone ER or patients can be switched from stable opioid therapies to hydromorphone ER without a loss of pain control.[11,13,17, 23-25] Additionally, it reduces break-

through pain (BTP) episodes, and maintains the analgesia for long treatment periods in patients with chronic malignant and nonmalignant pain. [11,13,17, 23-25] The safety and tolerability profiles of hydromorphone ER are consistent with other opioids, and the most commonly reported adverse events were nausea, constipation, somnolence, vomiting, headache, and dizziness for both cancer and noncancer pain.[7]

The other strong opioid alternative to morphine, oxycodone controlled-release (oxycodone CR), is a semisynthetic opioid analgesic. The recommended conversion ratio for oral oxycodone CR to oral morphine is 1:2.[2] As with hydromorphone ER, no ceiling effect is observed for treatment with oxycodone CR.[6] The oxycodone CR formulation used in this trial provides biphasic analgesia for 12 hours, with an immediate analgesic effect for 1 hour (38% of the dose) followed by a prolonged phase with the plasma half-life of 6.2 hour (62% of the dose).[14] Once-daily hydromorphone ER appears to have a comparable efficacy and safety profile as twice-daily oxycodone CR in the treatment of chronic noncancer pain.[1,10,20] Furthermore, the once-daily formulation of hydromorphone ER reduces the pill burden as compared with the twice-daily frequency of oxycodone CR formulation which may facilitate better adherence to the therapy. However, there is lack of data available on the comparison of these two treatments for the management of chronic cancer pain. Further, there are no reports on the efficacy and safety of hydromorphone ER for pain treatment in the Chinese population. Thus, this randomized, double-blind, multi-center, comparative, parallel-group study aimed to investigate the clinical noninferiority of efficacy of once-daily hydromorphone ER compared with twice-daily oxycodone CR for 28 consecutive days following completion of the dose-titration in Chinese patients with cancer pain.

Materials and Methods

Chinese patients aged 18-70 years (inclusive) who had inadequate control of moderate to severe cancer pain when receiving strong oral or transdermal opioid analgesics or who presented with cancer pain and were eligible to move to Step 3 of the WHO analgesic ladder when receiving weak opioids were included in the study. The study included patients who required or were expected to require between 40 mg and 184 mg of oral morphine or morphine equivalents every 24 hours for the chronic management of cancer pain and those who were reasonably expected to achieve a stable dose of opioid study medication during the study. Required life expectancy of patients was 12 weeks or longer.

Patients were excluded from the study if they had pure neuropathic pain or pain of unknown origin (where a mechanism or physical cause could not be identified), only had pain on movement or acute pain, required other opioid analgesics (apart from morphine HCl, in IR formulation, allowed as rescue medication for BTP), had any significant CNS disorder, and the risks of treatment with study medication could outweigh the potential benefits. Furthermore, women of childbearing potential who were pregnant or lactating were also excluded from the study.

The Independent Ethics Committee or Institutional Review Board at each study site approved the protocol and the study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practices and applicable regulatory requirements. All patients or their legally acceptable representatives provided written informed consent before entering the study.

Study design

This was a phase 3, randomized, double-blind, multicenter, comparative, parallel-group registration study conducted to demonstrate the clinical noninferiority of efficacy of once-daily oral hydromorphone ER compared with twice-daily oral oxycodone CR in patients with moderate to severe cancer pain. The study sites were chosen based on the following criteria: investigator was a cancer pain specialist with previous clinical trial experience, availability of sufficient human resources, reasonable recruitment rate estimation, and availability of equipment that can fulfill study requirements.The study consisted of 3 phases: a screening period (up to 14 days prior to randomization), a dose-titration phase (up to 8 days), and a 28-day dose maintenance phase. Upon entry into the dose-titration phase, randomized patients were converted from their prior opioids to their morphine equivalents (morphine : hydromorphone ER, 5:1; morphine : oxycodone CR, 2:1). Randomized patients were titrated to adequate effect (as determined by the pain assessments and supplementary analgesic requirements) and dosage adjustments were made no more frequently than every 2 days. Upward and downward dose-titrations were allowed, but the maximum total daily dose was not to exceed 32 mg hydromorphone ER or 80 mg oxycodone. For the BTP episodes observed in a 2-day period, BTP (rescue analgesic: morphine hydrochloride) medication was administered once every 4 hours as needed. Patients had to achieve a stable dose providing pain control (the use of BTP medications $\leq$ 3 times per day on average) at least in the last 2 days of the titration phase (2 days to 8 days) to be eligible to enter the maintenance phase, and this dose was continued for 28 consecutive days during the maintenance phase. In the maintenance phase, upward and downward dose-titrations were not to exceed a total daily dose of 32 mg hydromorphone ER or 80 mg oxycodone CR. Study visits were scheduled at weekly intervals (7±1 day) during this phase.

Randomization, blinding and treatment

Central randomization (1:1) by an online dynamic minimization allocation program (Interactive Web based Response System (IWRS) with center, concomitant cancer therapy (with or without chemotherapy or radiotherapy) and administration of opioids during the last 14 days before entry to the study (strong opioids/weak opioids) as the stratification factors was implemented. The IWRS designated a unique patient number and treatment code, which dictated the treatment assignment for each patient. The blind was broken only if specific emergency treatment dictated knowing the treatment status. In case an emergency unblinding was considered necessary, the investigator was to first contact the sponsor, and login to the IWRS to display the unblinded drug information. If the investigator was unable to contact the sponsor before unblinding due to an emergency situation, the sponsor was informed as soon as possible.

Hydromorphone ER (8 mg, 16 mg) (ALZA Corporation and Johnson & Johnson Pharmaceutical Research & Development), oxycodone CR (10 mg, 20 mg, and 40 mg) (Mundipharma Medical Company, and Johnson & Johnson Pharmaceutical Research & Development), and placebo were provided in the form of over-encapsulated tablets. Dosing had to start in the morning and the study drug was administrated twice-daily, with placebo tablet substituted for one dose of hydromorphone ER to maintain blinding. Morphine HCl, in IR tablet form (5 and 10 mg) (Qinghai Pharmaceutical Company Limited), was used as rescue medication. A single dose of rescue medication was approximately 15% of the corresponding total daily dose of study medication.

Prior and concomitant therapy

Opioids, other than the study drug and rescue medication, were not allowed during the study. In addition, the following therapies were not allowed during the study or within 2 weeks before entry: MAO inhibitors, neuro-ablative procedures, therapy with isotopes, anesthetic procedures including acupuncture, or surgical procedures relevant to cancer pain. Fentanyl patches were not allowed during the study or within 5 days before entry. All the above medications are analgesics and will impact pain assessment, and as the objective of the trial was to assess OROS hydromorphone analgesic efficacy and safety with the primary endpoint 'BPI worst pain in the past 24 hours', these medications were excluded. Adjuvant medications such as paracetamol, nonsteroidal anti-inflammatory drugs, anxiolytics, antidepressants, antiarrhythmic drugs, hormone therapy, corticosteroids, anticonvulsants, and neuroleptics were allowed only if, at study start, patient was on a stable dose, which was to be maintained.

Evaluations

Efficacy

A validated Chinese version of the rating scale Brief Pain Inventory (BPI) (Short Form) was used for evaluation of the intensity of pain (sensory dimension) and interference of pain in the patient's life (reactive dimension).[5] All items from the BPI (Short Form) scale were completed by the investigator at screening and each of the subsequent visits, before other trial assessments were performed or study medication was administered.

Primary efficacy parameter was patient assessment of 'pain at its worst in the past 24 hours', included as an item in the BPI Short Form (0 = no pain, 10 = pain as bad as the patient could imagine, at endpoint). Endpoint was defined as the last recorded BPI score of worst pain, just before taking the morning dose of study drug.

Secondary efficacy parameters were assessments of 'pain at its least in the past 24 hours', 'average pain', 'pain right now'(all measured on a scale of 0 to 10, where 0 = no pain, 10 = pain as bad as the patients could imagine), and 'pain relief in the past 24 hours'(presented as percentage, where 0% = no relief, 100% = complete relief), recorded in the BPI (Short Form) and BTP medication (rescue medication) intake. Patients recorded the time and number of study medication and rescue analgesic medication taken in the diaries.

Safety

Treatment-emergent adverse events (TEAEs), clinical laboratory tests (hematology, serum chemistry, and urinalysis), vital sign measurements, physical examinations, ECGs were assessed. TEAEs were either reported by the patient voluntarily or were obtained via patient interviews at study visits.

Statistical methods

Sample size determination

Assuming 2.5 as the variability (standard deviation [SD]), and the between-group difference in change from baseline of the BPI mean scores ("worst pain in the past 24 hours") as 0 at the end of the 28-day maintenance phase, with 90% power, the sample size needed was 60 patients per treatment group with noninferiority margin as 1.5 and 1-sided type I error rate of 0.025. Considering specific regulatory requirements in China (at least 100 patients per arm) and a 30% dropout rate, the sample size of 130 patients per treatment group (260 patients in total) was deemed appropriate.

Analysis sets

Full Analysis Set (FAS): All randomized patients with at least one dose of medication administered during the titration phase and at least one assessment of efficacy data were included in the FAS. Per Protocol Set (PPS): Patients who had completed all efficacy evaluations with good compliance, which was defined as the absence of reported protocol deviations that would have had a deleterious impact on the assessment of the efficacy of the study drugs. Safety Set (SS): All patients with at least one dose of study medication administered during the titration phase and at least one assessment of safety data.

Efficacy analyses

The primary endpoint was change from baseline in worst pain in the past 24 hours in BPI at the end of study for PPS population. The last observation carried forward (LOCF) (Last Observation prior to overdose rescue medication Carried Forward) was used when patients took more rescue medication and opioid therapy, or other opioid therapy than was allowed in the study. Post-hoc sensitivity analyses using the redefined PPS were conducted to assess the robustness of the primary analysis. The redefined PPS included 2 patients who were excluded from the PPS. One of these patients had completed the study and the other patient was originally excluded from the PPS because of a major protocol deviation (taking prolonged opioids on visit 1 [during the trial]); however, it was later confirmed that the patient started taking the study drug one day after stopping original opioid therapy, therefore this patient was included in the redefined PPS. Adjusted mean difference of the BPI score (‘worst pain in the past 24 hours’) for change from baseline between the 2 treatment groups was calculated based on analysis of covariance (ANCOVA).

All secondary analyses were conducted using the PPS and FAS. The point estimate and 2-sided 95% confidence intervals (CI) based on ANCOVA were provided for the difference between hydromorphone ER and oxycodone CR groups in the mean change from baseline at each visit and at the endpoint of pain at its least in the past 24 hours, pain on average, pain right now, and pain relief use in the past 24 hours. Wilcoxon rank-sum test was used for number of breakthrough pain medication doses taken. For safety, descriptive analyses were performed in the SS population. Median duration of persistence of TEAEs was calculated posthoc. The estimate of the hazards ratio (HR) and its 95% confidence interval was based on the Cox proportional hazards model with treatment as the only covariate.

Results

Of the 260 (130 in each group) patients randomized, 137 (hydromorphone ER: 70; oxycodone CR: 67) patients completed the maintenance phase of the study (Figure 1). The baseline characteristics were comparable between the 2 treatment groups, except in the hydromorphone ER group where a higher percentage of patients with bone metastasis (hydromorphone ER: 52.0%; oxycodone CR: 37.4%), and Eastern Cooperative Oncology Group (ECOG) performance status of 3 (hydromorphone ER: 25.6%; oxycodone CR: 18.7%) were observed (Table 1). The most common baseline ECOG performance status was 2 and the prior medications for both treatment groups were opioid analgesics (hydromorphone ER: 97 patients [75.8%]; oxycodone CR: 98 patients [77.8%]). Treatment compliance was comparable between the 2 treatment groups and the majority of patients had treatment compliance between 80% and 120%. The mean (SD) dose of study medication in the overall maintenance phase was 16.0 mg (8.51) in the

hydromorphone ER group and 38.5 mg (20.94) in the oxycodone CR group. A total of 200 patients (81.3%) reported pain at baseline. Baseline BPI scores (worst, least, average and now) and BPI pain interference scores were similar between the 2 treatment groups (Table 2).

Efficacy

Primary

The mean BPI score for 'pain at its worst in the past 24 hours', for hydromorphone ER versus oxycodone CR at baseline was 6.7 versus 6.9, which decreased to 4.9 versus 5.1 at study end. For the primary endpoint, the least-square (LS) mean difference between the 2 treatment groups was −0.1 with a 2-sided CI of (−1.3, 1.1). As the upper bound of the 2-sided 95% CI is less than the noninferiority margin of 1.5, hydromorphone ER is demonstrated to be noninferior to oxycodone CR (Table 3). Mean change from baseline of 'Worst pain in the past 24 hours overtime (PPS) is shown in figure 2. Results from the analysis based on the FAS (95% CI of the difference [−0.4, 0.7]) were consistent with the PPS analysis. Results of the post-hoc sensitivity analysis were consistent with the current FAS and PP analysis

Secondary

The results for the secondary parameters are summarized in figure 3A-D. The mean BPI score for 'pain at its least in the past 24 hours' for hydromorphone ER versus oxycodone CR decreased from baseline (2.4 versus 2.3) to study end (1.6 versus 1.9); the LS mean difference between the groups was −0.2 (95% CI of [−1.0, 0.6]). The mean BPI score for 'average pain in the past 24 hours' for hydromorphone ER versus oxycodone CR at baseline was 4.7 in both treatment groups and decreased at endpoint (2.9 versus 3.3); the LS mean difference between the groups

was −0.2 (95% CI [−1.1, 0.7]). The mean BPI score for 'pain right now' for hydromorphone ER versus oxycodone CR at baseline was 4.1 for both treatment groups and decreased at Ve (2.7 versus 2.8); the LS mean difference between groups was 0.1 (95% CI [−0.9, 1.1]). At baseline, 'pain relief in the past 24 hours', was similar in both groups (48.8%) and had improved (hydromorphone ER: 64.5%, oxycodone CR: 62.2%) at study end; the LS mean difference between groups was 5.8% (95% CI of [−5.3%, 16.8%]). The results of the secondary parameters were consistent with the primary endpoint outcome. The average number of doses of BTP medication taken was slightly lower in the hydromorphone ER group (24.2) than the oxycodone CR group (29.3) (Table 4).

Safety

A total of 111 (86.7%) patients in the hydromorphone ER group and 117 (92.9%) patients in the oxycodone CR group experienced at least one TEAE during the study (Table 5). The majority of TEAEs were mild or moderate in severity and incidences were similar in both treatment groups. The incidence of severe TEAEs was similar between the 2 treatment groups (hydromorphone: 30 patients [23.4%]; 30 patients [23.8%]). The overall incidence of serious TEAEs was numerically higher in the oxycodone CR group (18 patients, 14.3%) compared with the hydromorphone ER group (11 patients, 8.6%). Most serious TEAEs were reported in no more than one patient in each treatment group, The incidence of AEs leading to study treatment discontinuation was comparable between the 2 treatment groups (hydromorphone ER: 19 patients [14.8%]; oxycodone CR: 18 patients [14.3%]). Gastrointestinal disorders were the major reason for discontinuing study treatment due to TEAEs (hydromorphone ER: 8 [6.3%]; oxycodone CR: 6 [4.8%]). The most commonly reported TEAEs of special interest in the hydromorphone ER

versus oxycodone CR group were constipation (33.6% versus 35.7%), nausea (33.6% versus 35.7%), vomiting (33.6% versus 37.3%). Some patients had a co-occurrence of different TEAEs. Vomiting and nausea (hydromorphone ER: 26 [20.3%]; oxycodone CR: 32 [25.4%]), constipation and nausea (hydromorphone ER: 17 [13.3%]; oxycodone CR: 18 [14.3%]), and vomiting and constipation (hydromorphone ER: 13 [10.2%]; oxycodone CR: 18 [14.3%]) co-occurred in most patients; the percentage of patients who showed co-occurrence of these TEAEs was similar in both the treatment groups. There was no difference between hydromorphone ER versus oxycodone CR for HRs of duration (medians) of persistence of the most common TEAEs such as vomiting (4 days versus 5 days [HR: 0.813; 0.566, 1.168]), constipation (5 days versus 5 days [HR: 0.844; 0.548, 1.299]), nausea (5 days versus 5 days [HR: 0.900; 0.618, 1.310]), dizziness (5 days versus 3 days [HR: 1.200; 0.644, 2.238]), pyrexia (2 days versus 2 days [HR: 0.694; 0.435, 1.108]) and decreased appetite (10 days versus 10 days [HR: 1.088; 0.555, 2.134]). There were 24 deaths (hydromorphone ER: 8 patients [6.3%]; oxycodone CR: 16 patients [12.7%]) reported in this study; the most common reason for death was disease progression. There were no study drug-related deaths in either treatment group during the study.

Discussion

In this study, once-daily hydromorphone ER was noninferior to twice-daily oxycodone CR in treatment of moderate to severe cancer pain, as assessed by BPI score for ‘pain at its worst in the past 24 hours’. Both treatments resulted in similar improvements for other BPI pain severity outcome measures including ‘pain at its least in the past 24 hours’, ‘average pain’, ‘pain right now’, and ‘pain relief in the past 24 hours’, and rescue medication dose intake. These findings

corroborated those from an earlier study in patients with chronic pain associated with osteoarthritis of the knee or hip, wherein once-daily hydromorphone ER and twice-daily oxycodone CR demonstrated comparable relief of chronic moderate to severe pain.[10] Another study that used the BPI assessment for chronic pain showed that hydromorphone ER was noninferior to oxycodone CR (P = 0.011) as measured by change in BPI pain severity subscore 'pain right now' in patients with severe noncancer chronic pain requiring the continuous (24-weeks) use of strong opioids.[1] Furthermore, these patients (40.4% of the patients who completed the 24-week core phase study, hydromorphone ER: 60; oxycodone CR: 52) were allowed to continue in an extension phase of the study, and pain control was maintained in both groups for up to 1 year, with hydromorphone ER demonstrating a similar efficacy to oxycodone CR.[20] Also, favorable outcomes in other BPI items such as 'pain right now,' 'pain at its worst,' and 'pain at its least' were observed. Morphine is often still considered the gold standard of pain control and clinical equivalence for immediate-release formulation (2-9 days treatment) of hydromorphone and morphine was demonstrated in chronic cancer pain patients for 'worst pain in the past 24 hours' item of the BPI (primary endpoint). However, for the sustained-release formulations (10-15 days treatment) no equivalence was observed, and the direction of the difference was in favor of hydromorphone.[11] Furthermore, those patients who had successfully completed the short-term equivalence study and thereafter continued in a 1-year single-treatment extension study with hydromorphone showed that efficacy or safety in the long-term study were not affected by the prior opioid therapy in the short-term study, and that it was beneficial in the management of persistent, moderate-to-severe cancer pain.[12]

Earlier studies that had used a 5:1 (morphine to hydromorphone) morphine equianalgesic ratio conversion of prior opioid therapies to hydromorphone ER similar to the current study had also

demonstrated significant improvements in BPI ratings from prior opioid therapy to the end of hydromorphone ER therapy in chronic malignant and nonmalignant patients.[11,12,17,23,24] Taken together, these data were used to derive the optimal dose conversion ratio from prior opioid to hydromorphone ER in the current study. Beneficial reduction in pain severity with hydromorphone ER has been noted in moderate to severe cancer pain patients with all types of cancers, for treatment periods as short as 14 days (maintenance phase) to longer treatment periods of 1 year.[12,24] Therefore, the treatment maintenance period of 28 days chosen for the current study seems to be appropriate to gauge the treatment related favorable outcomes in our cancer pain population.

Of the 260 patients randomized equally into the 2 treatment groups, 248 patients were included in the FAS population and only 81 patients in the PPS (efficacy analysis set) as a large number of patients withdrew from the study or were noted to have protocol deviations. These protocol deviations were deviations of entry criteria, errors in treatment assignment, use of excluded medication (e.g., taking other prolonged-release opioids analgesics during the trial, or taking other opioid analgesics within 24 hours prior to or through end-of-study BPI) or entered into the maintenance phase incorrectly. However, certain protocol deviations after use of disallowed concomitant medication were deemed to have less of an impact on the efficacy assessments included: patients who received non-study-specified opioid analgesics as rescue medication, or those who were taking maximum dosage of study drug and >3 requirements of rescue medication, rescue medication plus other opioids analgesics, or other opioids analgesics in 2 consecutive days, at any time during the maintenance phase and 24 hours prior to endpoint BPI. Patient with such protocol deviations were included in the PPS. The proportion of patients in the 2 treatment groups that had major protocol deviations was comparable. Further, the study was

amended to analyze the primary and secondary endpoints based on the "redefined" LOCF using the PPS where specified. The "redefined" LOCF was applied to exclude measurements obtained after patients took more rescue medication and opioid therapy, or other opioid therapy than was allowed in the study because we were concerned that excess of rescue medication and opioid therapy will impact study drug and comparator efficacy, or in other words it would increase study drug or comparator's true analgesic effect. However, the redefined results may reflect the appropriate effect of study drug and comparator.

The percentage of completers in each phase of the study was comparable in the 2 treatment groups. In the maintenance phase of the study, usage of doses higher than the maximum dosage allowed was the most common reason for discontinuation of study drug in the hydromorphone ER group and safety was the most common reason for discontinuation of study drug in the oxycodone CR group. The overall safety and tolerability profile observed in this study was good and generally consistent with previous trials with hydromorphone ER in cancer patients.[12,17,24-25] Severity of TEAEs was assessed by the investigator per definitions based on ICH guidelines for GCP which are routinely used in clinical trials of drugs.The majority TEAEs were mild or moderate in severity and the incidence of TEAEs was slightly higher for patients in the oxycodone CR group compared with the hydromorphone ER group. The most common TEAEs were nausea, vomiting, and constipation, which are consistent with the known TEAE profile of hydromorphone ER and oxycodone CR in patients with chronic cancer and noncancer pain.[1,10,12,24] Furthermore, the duration of perisistence of the most common TEAEs was similar in both the treatment groups. The incidence of serious TEAEs was higher in the oxycodone CR group. There were 24 deaths in the study, the most common reason resulting from disease progression, consistent with other cancer patient trials. Overall, the safety profiles for both

treatment groups were comparable and there were no emerging safety concerns for hydromorphone ER in this study.

A limitation of the study was that, only 31% of the randomized patients were included in the PPS population (efficacy analysis set) for the noninferiority analysis between the 2 treatment groups. However, the results from the analysis performed on the FAS population, which consisted of 95% of the randomized patients, were consistent with the PPS population analysis. The other limitation was the use of LOCF for the primary efficacy analyses, which may potentially bias the estimated treatment effect. In conclusion, once-daily hydromorphone ER (8-32 mg) was noninferior to twice-daily oxycodone CR (10-40 mg) in alleviating cancer pain and the safety profiles were comparable between the two treatment groups, supporting the concept that a treatment option exists for healthcare providers and patients, with the potential for a reduced dosing frequency.

Acknowledgements

We thank the study participants, without whom this study would never have been accomplished, and the following investigators for their participation in this study: Drs.Jinji Yang, People's Hospital of Guangdong Province; Huiqiang Huang, Sun Yat-Sen University Cancer Center; Shikai Wu, 307 Hospital of PLA; Jian Luo, Cancer Institute 7 Hospital, Chinese Academy of Medical Sciences; Wei Shen, Xin Hua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine; Yajie Wang, Shanghai Changhai Hospital; Hongming Pan, Sir Run Run Shaw Hospital, School of Medicine, Zhejiang University; Cheng Huang, Cancer Hospital of Fujian Province; Guangru Xie, Tianjian Medical University Cancer Institute and Hospital; Zhendong Chen, The First Affiliated Hospital of Anhui Medical University; Jiejun Wang,

Shanghai Changzheng Hospital; Feng Bi, West China Hospital of Sichuan University; Jianping Xiong, The First Affiliated Hospital of Nanchang University; Wenwu Cheng, Fudan University Shanghai Cancer Center; Xiaohua Hu, Cancer Hospital of Guangxi Province; Gang Wu and Jing Cheng, Union Hospital of Tongji Medical College of Huazhong University of Science and Technology.

The authors also thank Drs.Wenyu Gu, Ute Richarz and Bruce Xue (Janssen Research & Development, LLC) for their contributions to the design of this study, Dr. Sangita P. Patil (SIRO Clinpharm Pvt. Ltd.) for providing writing assistance and Dr. Wendy P. Battisti (Janssen Research & Development, LLC) for providing additional editorial support and review for this manuscript.

Study support: Funded by Janssen Research & Development, LLC., New Jersey, USA

Disclosures

The study was funded by Janssen Research & Development, LLC., New Jersey, USA. Dr. Lu Yu, and Ms Yanyan Hou, are employees of Xi'an Janssen Pharmaceutica, China, and Drs. Han and Richards are employees of Janssen Research & Development, LLC., New Jersey, USA.

Dr. Shiying Yu was the leading investigator of the trial, reviewed database and all versions of the article. Dr. Wei Shen was a significant investigator of the trial, and reviewed all versions of the article. Dr. Lu Yu was the trial responsible physician of the trial, reviewed database and all versions of the article. Dr John Han and Ms Yanyan Hou were responsible for data collection and analysis. Dr Henry Richards made substantial contributions to acquisition of data, medical

review of data, and analysis and interpretation of data, including authorship of the CSR All authors met ICMJE criteria and all those who fulfilled those criteria are listed as authors. All authors had access to the study data, provided direction and comments on the manuscript, and made the final decision about where to present these data.

References

1. Binsfeld H, Szczepanski L, Waechter S, Richarz U, Sabatowski R: A randomized study to demonstrate noninferiority of once-daily OROS((R)) hydromorphone with twice-daily sustained-release oxycodone for moderate to severe chronic noncancer pain. Pain Pract 10:404-415, 2010

2. Bruera E, Belzile M, Pituskin E, Fainsinger R, Darke A, Harsanyi Z, Babul N, Ford I: Randomized, double-blind, cross-over trial comparing safety and efficacy of oral controlled-release oxycodone with controlled-release morphine in patients with cancer pain. J Clin Oncol 16:3222-3229, 1998

3. Cancer pain relief: with a guide to opioid availability - 2nd ed. World Health Organization. 1996

4. Claxton AJ, Cramer J, and Pierce C: A systematic review of the associations between dose regimens and medication compliance. Clin Ther 23:1296-1310, 2001

5. Cleeland CS, Ryan KM: Pain assessment: global use of the Brief Pain Inventory. Ann Acad Med Singapore 23:129-138, 1994

6. Coluzzi F, Mattia C: Oxycodone. Pharmacological profile and clinical data in chronic pain management. Minerva Anestesiol 71:451-460, 2005

7. Coluzzi F, Mattia C: OROS(R) hydromorphone in chronic pain management: when drug delivery technology matches clinical needs. Minerva Anestesiol 76:1072-1084, 2010

8. Drover DR, Angst MS, Valle M, Ramaswamy B, Naidu S, Stanski DR, Verotta D: Input characteristics and bioavailability after administration of immediate and a new extended-release formulation of hydromorphone in healthy volunteers. Anesthesiology 97:827-836, 2002

9. Ferrell B, Wisdom C, Wenzl C, Brown J: Effects of controlled-released morphine on quality of life for cancer pain. Oncol Nurs Forum 16:521-526, 1989

10. Hale M, Tudor IC, Khanna S, Thipphawong J: Efficacy and tolerability of once-daily OROS hydromorphone and twice-daily extended-release oxycodone in patients with chronic, moderate to severe osteoarthritis pain: results of a 6-week, randomized, open-label, noninferiority analysis. Clin Ther 29:874-888, 2007

11. Hanna M, Thipphawong J:. A randomized, double-blind comparison of OROS(R) hydromorphone and controlled-release morphine for the control of chronic cancer pain. BMC Palliat Care 7:17, 2008

12. Hanna M, Tuca A, Thipphawong J: An open-label, 1-year extension study of the long-term safety and efficacy of once-daily OROS(R) hydromorphone in patients with chronic cancer pain. BMC Palliat Care 8:14, 2009

13. Lee KH, Kim MK, Hyun MS, Kim JY, Park KU, Song HS, Lee SA, Lee WS, Bae SH, Ryoo HM, Cho YY: Clinical effectiveness and safety of OROS(R) hydromorphone in break-through cancer pain treatment: a multicenter, prospective, open-label study in Korean patients. J Opioid Manag 8:243-252, 2012

14. Mandema JW, Kaiko RF, Oshlack B, Reder RF, Stanski DR: Characterization and validation of a pharmacokinetic model for controlled-release oxycodone. Br J Clin Pharmacol 42:747-756, 1996

15. Nathanson IT, Daland EM: The Use of Dilaudid in Treating Patients with Cancer. New England Journal of Medicine 213(16):741-746, 1935

16. O'Neill B, Fallon M: ABC of palliative care. Principles of palliative care and pain control. BMJ 315:801-804, 1997

17. Palangio M, Northfelt DW, Portenoy RK, Brookoff D, Doyle RT, Jr., Dornseif BE, Damask MC: Dose conversion and titration with a novel, once-daily, OROS osmotic technology, extended-release hydromorphone formulation in the treatment of chronic malignant or nonmalignant pain. J Pain Symptom Manage 23:355-368, 2002

18. Palliative Care. Cancer control : knowledge into action : WHO guide for effective programmes ; module 5. World Health Organization, 2007

19. Quigley C: Hydromorphone for acute and chronic pain. Cochrane Database Syst Rev(1):CD003447, 2002

20. Richarz U, Waechter S, Sabatowski R, Szczepanski L, Binsfeld H: Sustained safety and efficacy of once-daily hydromorphone extended-release (OROS(R) hydromorphone ER) compared with twice-daily oxycodone controlled-release over 52 weeks in patients with moderate to severe chronic noncancer pain. Pain Pract 13:30-40, 2013

21. Riley J, Ross JR, Rutter D, Wells AU, Goller K, du Bois R, Welsh K: No pain relief from morphine? Individual variation in sensitivity to morphine and the need to switch to an alternative opioid in cancer patients. Support Care Cancer 14:56-64, 2006

22. Sarhill N, Walsh D, Nelson KA: Hydromorphone: pharmacology and clinical applications in cancer patients. Support Care Cancer 9:84-96, 2001

23. Wallace M, Rauck RL, Moulin D, Thipphawong J, Khanna S, Tudor IC: Once-daily OROS hydromorphone for the management of chronic nonmalignant pain: a dose-conversion and titration study. Int J Clin Pract 61:1671-1676, 2007.

24. Wallace M, Rauck RL, Moulin D, Thipphawong J, Khanna S, Tudor IC: Conversion from standard opioid therapy to once-daily oral extended-release hydromorphone in patients with chronic cancer pain. J Int Med Res 36:343-352, 2008

25. Wallace M, Moulin DE, Rauck RL, Khanna S, Tudor IC, Skowronski R, Thipphawong J: Long-term safety, tolerability, and efficacy of OROS hydromorphone in patients with chronic pain. J Opioid Manag 5:97-105, 2009

Figure legends

Figure 1. Study design and patient disposition (All randomized patients)

Figure 2. Mean Change in Pain at its Worst in the Past 24 hours Overtime (Per Protocol Set)

Figure 3. Mean Change in A) Pain at its Least in the Past 24 hours, B) Pain on Average in the Past 24 hours, C) Pain Right Now, and D) Pain Relief in the Past 24 hours Over Time - (Per Protocol Set)

Table 1. Demographics and baseline characteristics (Full Analyses Set)

Demographics	**Hydromorphone ER (N = 125)**	**Oxycodone CR (N = 123)**
Age (years)		
Category, n (%)		
< 60	82 (65.6)	88 (71.5)
≥ 60	43 (34.4)	35 (28.5)
Mean (SD)	53.5 (10.86)	52.7 (10.75)
Median	54.0	55.0
Range	(22; 70)	(18; 68)
Sex, n (%)		
Men	82 (65.6)	80 (65.0)
Women	43 (34.4)	43 (35.0)
Cancer diagnosis		
Breast	8 (6.4)	7 (5.7)
Lung	38 (30.4)	34 (27.6)
Bone	0 (0)	0 (0)
Oral cavity	1 (0.8)	0 (0)
Gastrointestinal	46 (36.8)	46 (37.4)
Genitourinary	13 (10.4)	17 (13.8)
Lymphoma	0 (0)	0 (0)
Leukemia	0 (0)	0 (0)
Other	17 (13.6)	16 (13.0)
Not known	2 (1.6)	3 (2.4)
Tumor metastatic (yes or no)		
Yes	118 (94.4)	112 (91.1)
No	7 (5.6)	11 (8.9)
Tumor metastatic site[a]		
None	7 (5.6)	11 (8.9)
Brain	9 (7.2)	13 (10.6)
Bone	65 (52.0)	46 (37.4)
Bone marrow	1 (0.8)	1 (0.8)

Lung	30 (24.0)	24 (19.5)
Liver	31 (24.8)	26 (21.1)
Kidney	0 (0.0)	0 (0.0)
Lymph node	53 (42.4)	53 (43.1)
Other	32 (25.6)	39 (31.7)
ECOG performance status		
0	1 (0.8)	2 (1.6)
1	47 (37.6)	38 (30.9)
2	43 (34.4)	58 (47.2)
3	32 (25.6)	23 (18.7)
4	2 (1.6)	2 (1.6)
5	0 (0.0)	0 (0.0)
Concomitant cancer therapy		
With	75 (60.0)	72 (58.5)
Administration of opioids		
Strong opioids	104 (83.2)	105 (85.4)
Weak opioids	21 (16.8)	18 (14.6)
Treatment compliance, N	70	67
≥ 80%, ≤ 120%	67 (95.7)	64 (95.5)

CR: controlled-release; ECOG: Eastern Cooperative Oncology Group; ER: extended-release
[a] Tumor metastatic site – A multiple answer question

Table 2. Baseline Pain and Brief Pain Inventory Assessments (Full Analyses Set)

Baseline Number, n (%)	Hydromorphone ER (N = 125)	Oxycodone CR (N =123)
Pain at baseline[a], n (%)	124	122
Yes	101 (81.5)	99 (81.1)
No	23 (18.5)	23 (18.9)
BPI pain severity score (4 items)		
Pain at its worst, in the past 24 hours, N	124	122
Mean (SD)	6.5 (2.07)	6.3 (1.92)
Median	7.0	7.0
Range	(0; 10)	(0; 10)
Pain at its least, in the past 24 hours, N	124	122
Mean (SD)	2.3 (1.77)	2.1 (1.45)
Median	2.0	2.0
Range	(0; 8)	(0; 6)
Pain on average, N	124	122
Mean (SD)	4.4 (1.68)	4.3 (1.59)
Median	5.0	4.0
Range	(0; 9)	(0; 9)
Pain right now, N	124	122
Mean (SD)	4.0 (2.39)	3.7 (2.13)
Median	4.0	3.0
Range	(0; 10)	(0; 10)
Amount of pain relief		
Pain relief, in the past 24 hours, %, N	123	121
Mean (SD)	53.6 (26.28)	55.8 (24.92)
Median	60.0	60.0
Range	(0; 100)	(0; 100)

N = number of patients in the FAS; n = number of observations; SD = standard deviation
[a] Pain other than everyday kinds of pain at baseline

Table 3. Least Square Mean Changes from Baseline of Pain at its Worst in the Past 24 hours Score in Brief Pain Inventory (Per Protocol Set)

	Change from Baseline LSM (SE)			Between-group Difference *		ANCOVA	
Group	**N**	**LSM**	**SE**	**LSM (SE)**	**95% CI**	**Covariant**	***P-Value***
End of Study Ve							
Hydromorphone ER	40	−1.8	0.52	-		Baseline	<0.001
Oxycodone CR	41	−1.7	0.61	−0.1 (0.60)	−1.3, 1.1	Treatment	0.855
						Center	0.075

ANCOVA: Analysis of Covariance; CI: confidence interval; CR: controlled-release; ER: extended-release; LSM: least square mean; SE: standard error; Ve; end of study visit

* Between group difference = hydromorphone ER – oxycodone CR

Table 4. Number of Breakthrough Pain Medication (Rescue Medication) Doses Taken (Per Protocol Set)

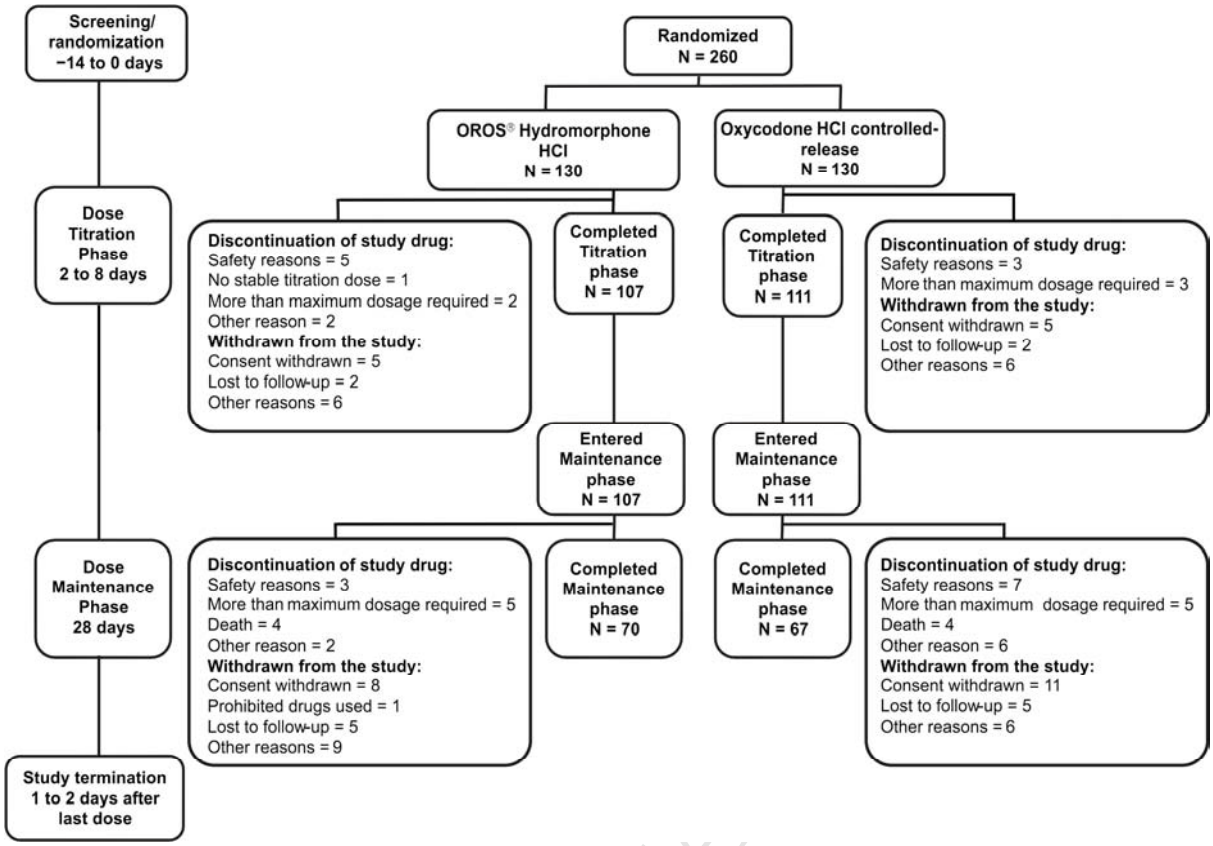
Group	N	Mean	SD	Median	Range	Between-group * Statistics	*P* Value
Overall maintenance phase							
Hydromorphone ER	36	24.2	24.41	20.0	(0; 80)		
Oxycodone CR	40	29.3	24.33	26.5	(0; 91)	Z = −1.089	0.276

CR: controlled-release; ER: extended-release; SD: standard deviation

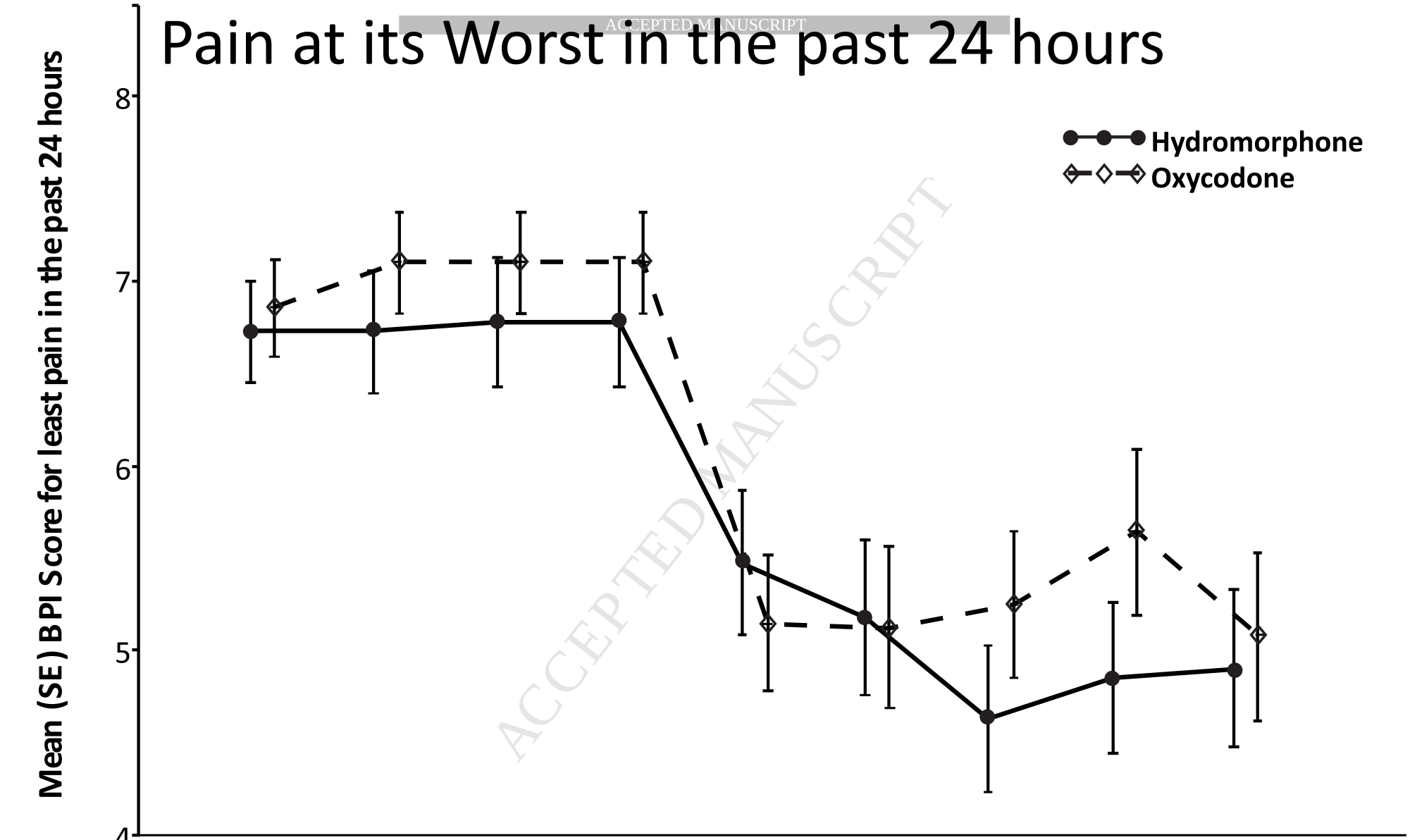
Table 5. Treatment-Emergent Adverse Events in at least 5% of patients – (Safety Set)

	Hydromorphone ER (N = 128) n (%)	**Oxycodone CR (N = 126)** n (%)
Any TEAE	**111 (86.7)**	**117 (92.9)**
Any AEs in at least 5% of patients in any treatment group	**102 (79.7)**	**107 (84.9)**
Vomiting	43 (33.6)	47 (37.3)
Constipation	43 (33.6)	45 (35.7)
Nausea	43 (33.6)	45 (35.7)
Pyrexia	24 (18.8)	27 (21.4)
Dizziness	21 (16.4)	22 (17.5)
Decreased appetite	20 (15.6)	21 (16.7)
White blood cell count decreased	13 (10.2)	17 (13.5)
Anemia	14 (10.9)	14 (11.1)
Decreased appetite	20 (15.6)	21 (16.7)
Diarrhea	12 (9.4)	9 (7.1)
Asthenia	11 (8.6)	9 (7.1)
Edema peripheral	11 (8.6)	6 (4.8)
Bone marrow failure	9 (7.0)	9 (7.1)
Chest discomfort	9 (7.0)	6 (4.8)
Hypoproteinemia	9 (7.0)	5 (4.0)
Platelet count decreased	8 (6.3)	7 (5.6)
Hyperhidrosis	3 (2.3)	8 (6.3)
Abdominal discomfort	4 (3.1)	7 (5.6)
Abdominal distension	7 (5.5)	7 (5.6)
Urinary tract infection	4 (3.1)	7 (5.6)
Neutrophil count decreased	7 (5.5)	5 (4.0)
Rash	7 (5.5)	4 (3.2)

AE = adverse event; CR: controlled-release; ER: extended-release



Pain at its Worst in the past 24 hours



	Vt1	Vt2	Vt3	Vt4	Vm1	Vm2	Vm3	Vm4	Ve
Hydromorphone	N=40	N=40	N=40	N=40	N=40	N=40	N=40	N=40	N=40
Oxycodone	N=41	N=41	N=41	N=41	N=41	N=41	N=41	N=41	N=41