

## ORIGINAL ARTICLE

# A phase III randomized controlled study on the efficacy and improved bowel function of prolonged-release (PR) oxycodone-naloxone (up to 160/80 mg daily) vs oxycodone PR

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## Conflicts of Interest

D. Dupouiron: Investigator in this study. He was contributor in seminars and workshops for Medtronic, Eisai, Astellas. A. Stachowiak: Investigator in this study. O. Loewenstein: took part in Phase II and Phase III studies as well as in NIS for Mundipharma, Allergan, Gruenthal, Servier. He was contributor in seminars and workshops for Mundipharma, Gruenthal, Allergan, Bastian, Eisai, Beta-Pharm, Pfizer, Teva. A. Ellery: Investigator in this study. W. Kremers, B. Bosse and M. Hopp are employees of Mundipharma Research GmbH & Co. KG.

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## 1. Introduction

The principle treatment for the management of moderate to severe pain, including cancer and non-cancer pain, involves opioid analgesia, with long-acting

or prolonged-release agents. Oxycodone in a prolonged-release (PR) formulation (OxyPR) was introduced to the market in 1995 and is now available in more than 50 countries for the treatment of

## Abstract

**Background:** Oxycodone/naloxone (OXN PR) is a prolonged-release formulation containing oxycodone and naloxone in a 2:1 ratio. This study aimed to evaluate the tolerability and efficacy of doses up to OXN160/80 mg PR compared with oxycodone prolonged-release formulation (OxyPR) in a randomised controlled trial.

**Methods:** Two hundred and forty-three patients were randomised to treatment with OXN PR ( $n = 123$ ) or OxyPR ( $n = 120$ ) during the 5-week double-blind study. Measured were: opioid-induced constipation [bowel function index score (BFI)]; analgesic efficacy (NRS 0–10); daily laxative rescue medication use; rescue medication use, and the number of complete spontaneous bowel movements (CSBMs) per week. A subanalysis was conducted in cancer patients.

**Results:** Greater reductions in mean BFI scores were reported for the OXN PR group compared with OxyPR from Week 1 onwards; at Week 5 the mean change from baseline was  $-32.5$  versus  $-14.2$ . Average 24-h pain scores were low and remained stable in the range 3–4 in both treatment groups. Analgesic rescue medication use was similar between the groups. Patients receiving OXN PR used significantly lower mean daily doses of laxative rescue medication than those receiving OxyPR ( $P = 0.006$ ). The number of CSBM in the OXN PR group approximately doubled compared with a 25% decrease in the OxyPR group. Comparable results to the total study population were reported in the cancer patient subgroup.

**Conclusions:** OXN PR in daily doses of up to 160/80 mg significantly improves bowel function compared with equivalent doses of OxyPR while still providing comparable analgesic efficacy.

**Significance:** Effective analgesia can be achieved using oxycodone/naloxone PR up to 160/80 mg daily without compromising bowel function. A similar outcome was reported in cancer and non-cancer patients.

moderate to severe pain. One issue with these agents is the occurrence of opioid-induced constipation, which results from the activation of the local  $\mu$ -opioid receptors in the gut (De Schepper et al., 2004). This in turn inhibits excitatory and inhibitory neural pathways within the enteric nervous system controlling motility (Linn and Steinbrook, 2007). The consequences of this action are a delay in gastric emptying, reduced fluid secretion and a slowing down of intestinal transit. The clinical consequences include infrequent and hard stool, straining, painful and incomplete bowel evacuation, bloating and abdominal cramping.

Constipation can cause patients to discontinue their treatment or lead to dose reductions, both of which can result in reduced analgesic efficacy. A number of approaches to relieve this form of constipation have been attempted including laxative use, but these do not focus on the mechanism of action of the opioids and have limited efficacy (Cherny et al., 2001). In contrast to the opioid analgesics, which act primarily as  $\mu$  receptor agonists, naloxone acts as full opioid receptor antagonist. Intravenous administration causes a reversal of all central and peripheral actions of the opioids (Meissner et al., 2000). Following oral administration naloxone acts locally in the gut to inhibit enteric opioid receptors but due to the considerable elimination from extensive first-pass hepatic metabolism, there is minimal systemic bioavailability and peripheral activity is reduced considerably (Fishman et al., 1973). As such, naloxone represents a causal treatment of opioid-induced constipation through its antagonist effect at the gastrointestinal opioid receptor. Another option is the peripherally acting  $\mu$  opioid receptor antagonists (PAMORAs).

Oxycodone/naloxone (OXN PR) is a prolonged-release formulation containing oxycodone and naloxone in a 2:1 ratio. This fixed combination was shown in a Phase II study to provide sufficient analgesic effect of oxycodone and was well tolerated, with no unexpected adverse events (Meissner et al., 2009). The results from Phase I–III studies (Simpson et al., 2008; Vondrackowa et al., 2008; Löwenstein et al., 2009) led to the product being released in 2006 and it is now available in different dose strengths for twice daily use. During the clinical developmental programme on OXN PR it was shown that although the approved dose range at that time of OXN80/40 mg PR per day was sufficient to manage a significant segment of the population of patients with severe pain, it was evident that there was a need for doses higher than OXN80/40 mg PR

per day in certain patients. Patients were also allowed to take OXN PR together with up to 400 mg OxyPR, taking into consideration the maximum daily dose of 400 mg oxycodone per day. It was considered that this extra dosing of oxycodone might impair the effects of naloxone. This study aimed to evaluate the tolerability and efficacy of doses up to OXN160/80 mg PR compared with OxyPR in a randomised controlled trial.

## 2. Materials and methods

### 2.1 Study design

This Phase III randomised double-blind study (ClinicalTrials.gov identifier NCT01438567) was designed to confirm improvement in bowel function, analgesic efficacy and safety profile of OXN PR in daily doses up to OXN160/80 mg PR compared with OxyPR in patients with non-malignant or malignant pain requiring opioids and opioid-induced constipation. The study was conducted in accordance with standard operating practices of the Sponsor and Contract Research Organisation (CRO), which ensure adherence to Good Clinical Practice (GCP) guidelines.

The study comprised of three phases: a pre-randomisation phase consisting of a screening period and a run-in period, a double-blind phase and an extension phase (Fig. 1). Eligible patients selected during the screening phase entered the Run-in phase, during which OxyPR was titrated to analgesic effect to determine the starting dose to be used after randomisation. At Visit 2 (V2), opioid therapy was converted to open-label OxyPR and titrated to an effective analgesic dose between OxyPR 100–160 mg (50, 60, 70 or 80 mg twice daily). Patients were provided with immediate-release oxycodone (OxyIR) for breakthrough pain to be used up to six times per day at a dose of approximately 1/6 that of the total daily study medication, and oral bisacodyl 10 mg/day as laxative rescue medication. Patients were also given a daily diary to record analgesic rescue medication use, laxative rescue medication use, bowel function measures and average pain over last 24 h.

These patients had to be on a stable dose of OxyPR twice daily for at least 4 consecutive days prior to randomisation and have a pain score of  $\leq 4$  with no more than two doses of OxyPR analgesic rescue medication per day for either the last 3 consecutive days or 4 of the last 7 days. Patients were randomly assigned in a 1:1 ratio to OXN PR or OxyPR for up to 5 weeks. The starting dose during the double-blind phase was dependent on the effective, stable

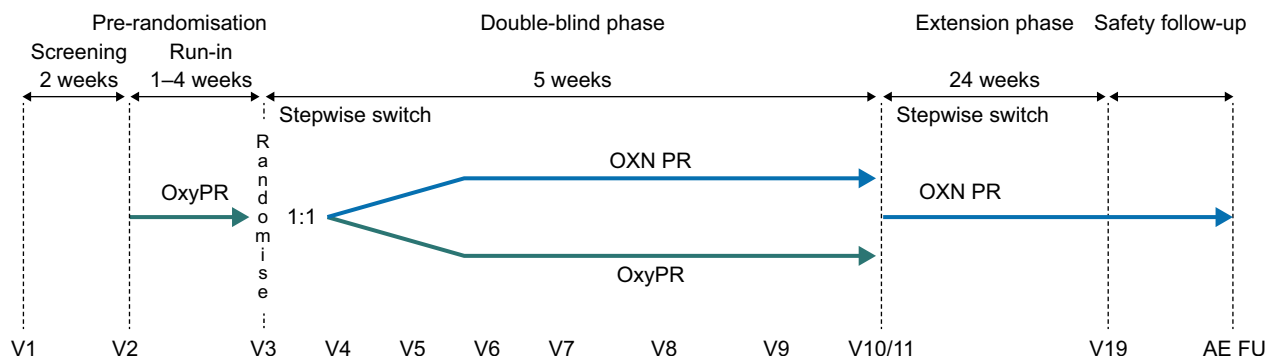


Figure 1 Study design.

analgesic dose established in the run-in period, but titration up to maximum daily dose of OXN PR 160/80 mg was permitted after 1 week.

## 2.2 Study endpoints

There were two primary objectives, the first of which was to demonstrate that patients taking OXN PR had improvement in symptoms of constipation as measured by the Bowel Function Index (BFI) compared with patients taking OxyPR tablets alone. The second was to demonstrate non-inferiority of OXN PR compared with OxyPR with respect to the analgesic efficacy based on average pain over last 24 h as measured by the Pain Intensity Scale. Secondary objectives included: analgesic and laxative rescue medication; complete spontaneous bowel movements (CSBMs); and quality of life (EuroQol EQ-5D-3L).

## 2.3 Patients

Enrolled patients were males and females aged  $\geq 18$  years with cancer and non-cancer pain requiring opioids according to World Health Organization (WHO) step III criteria and suffering from opioid-induced constipation caused or aggravated by opioids. Included patients were dissatisfied with their current analgesic medication due to lack of efficacy or unacceptable tolerability. The need for analgesic medication was defined as a documented history of requiring around-the-clock opioid therapy (100–160 mg OxyPR per day) for at least 5 weeks. Constipation caused or aggravated by opioids was confirmed by the patient and the investigator as an effect of the patient's pre-study opioid medication (at a comparable dose) and evidenced by a medical need of regular intake of laxatives to have at least three bowel evacuations per week or by having less than three bowel evacuations when not taking a laxative.

Non-analgesic concomitant medications, including those medications for the treatment of depression, and the non-opioid analgesic medication dose were required to be stable at screening and to have remained stable throughout the double-blind phase of the study, as judged by the investigator.

Exclusion criteria included: history of hypersensitivity to oxycodone, naloxone, related products or other ingredients of the study medications; any contraindication to bisacodyl or any components of the study medications; active alcohol or drug abuse and/or history of opioid abuse; unreported illicit drug use (including cannabis); any condition in which opioids are contraindicated. Patients were also excluded if they had taken naloxone  $\leq 30$  days prior to the start of the screening period or at screening; if they were taking or had taken monoamine oxidase inhibitors  $\leq 2$  weeks prior to the start of the screening period; or if they were suffering from diarrhoea.

## 2.4 Assessments

Patients were assessed at weeks 1, 2, 4 and 5 during the double-blind phase (at study site/home). Opioid-induced constipation was assessed using the BFI, daily laxative rescue medication use, and the number of CSBMs per week. The BFI score was the mean of the following three items subjectively assessed by the patient at each clinic visit: ease of defecation (numerical analogue scale (NAS), 0 = easy/no difficulty; 100 = severe difficulty), feeling of incomplete bowel evacuation (NAS, 0 = not at all, 100 = very strong), and judgement of constipation (NAS, 0 = not at all, 100 = very strong). Analgesic efficacy was measured as average pain over the last 24 h based on the Pain Intensity Scale (a numerical rating scale 0–10 in which 0 = no pain and 10 = worst imaginable pain) assessed at each visit and in patient daily diaries, together with analgesic rescue medication use. Quality of life (QoL) was evaluated using

the EuroQol EQ-5D-3L instrument. Adverse events were monitored throughout the 5-week study.

## 2.5 Statistical analyses

For the primary analysis of BFI endpoint, a mixed model repeated measures (MMRM) analysis of covariance of the BFI scores was carried out with no missing data imputation. The repeated measures analysis included fixed-effect terms for treatment and time, random effect for centre or site, and pre-randomisation value at the end of the Baseline Period. The same statistical MMRM model as used for the BFI was applied to analyse the Pain Intensity Scale results for average pain over last 24 h at each visit. The superiority analysis on the BFI was performed using the full analysis population (patients who were randomised and received at least one dose of study medication during the double-blind phase and who had at least a 1 week double-blind assessment of BFI). The non-inferiority test on the Pain Intensity Scale was performed using the per protocol population (patients who received at least 4 weeks study medication during the double-blind phase and who sufficiently complied with the study protocol). Superiority hypothesis tests applied a 5% two-sided significance level, while non-inferiority tests used a 2.5% one-sided significance level.

All secondary efficacy analyses were performed in an exploratory way using the full analysis population. For analgesic rescue medication intake, an additional analysis on per protocol population was also performed. Safety data were evaluated for all patients who received study drug and for whom at least one post-dose safety assessment was recorded.

A subgroup analysis of all cancer patients (with or without cancer-related pain) included in the study was conducted in an exploratory manner providing descriptive statistics and exploratory *P*-values to compare the treatment groups. All statistical analyses were performed using SAS<sup>®</sup> version 9.3 or later for Windows software package (SAS Institute, Cary, NC, USA).

## 3. Results

### 3.1 Patients

A total of 363 patients were enrolled and screened at 66 clinical centres in 11 countries. Of these, 243 patients were randomly assigned to treatment with OXN PR (*n* = 123) or OxyPR (*n* = 120). In total, 209 patients completed the study; 105 patients in the OXN PR group and 104 patients in the OxyPR group

(Fig. 2). After blinded subject evaluability review the following patient populations were available for analysis in the two treatment groups: full analysis, *n* = 121 OXN PR and *n* = 116 OxyPR; per protocol, *n* = 93 OXN PR and *n* = 99 OxyPR; and safety, *n* = 123 OXN PR and *n* = 120 OxyPR.

Baseline patient characteristics of the randomised population are shown in Table 1. Nearly, all patients were taking at least one concomitant medication. Just over half of patients (51.0%) were taking medications for disorders of the alimentary tract and metabolism (Table 2). Consistent with the frequency of musculoskeletal and connective tissue disorders, many patients were taking medications for musculoskeletal symptoms. Non-steroidal anti-inflammatory and anti-rheumatic agents were the most frequently used medications in this therapeutic class.

### 3.2 Study medication

The numbers of patients at each dosing level in the two treatment groups were similar (Table 3).

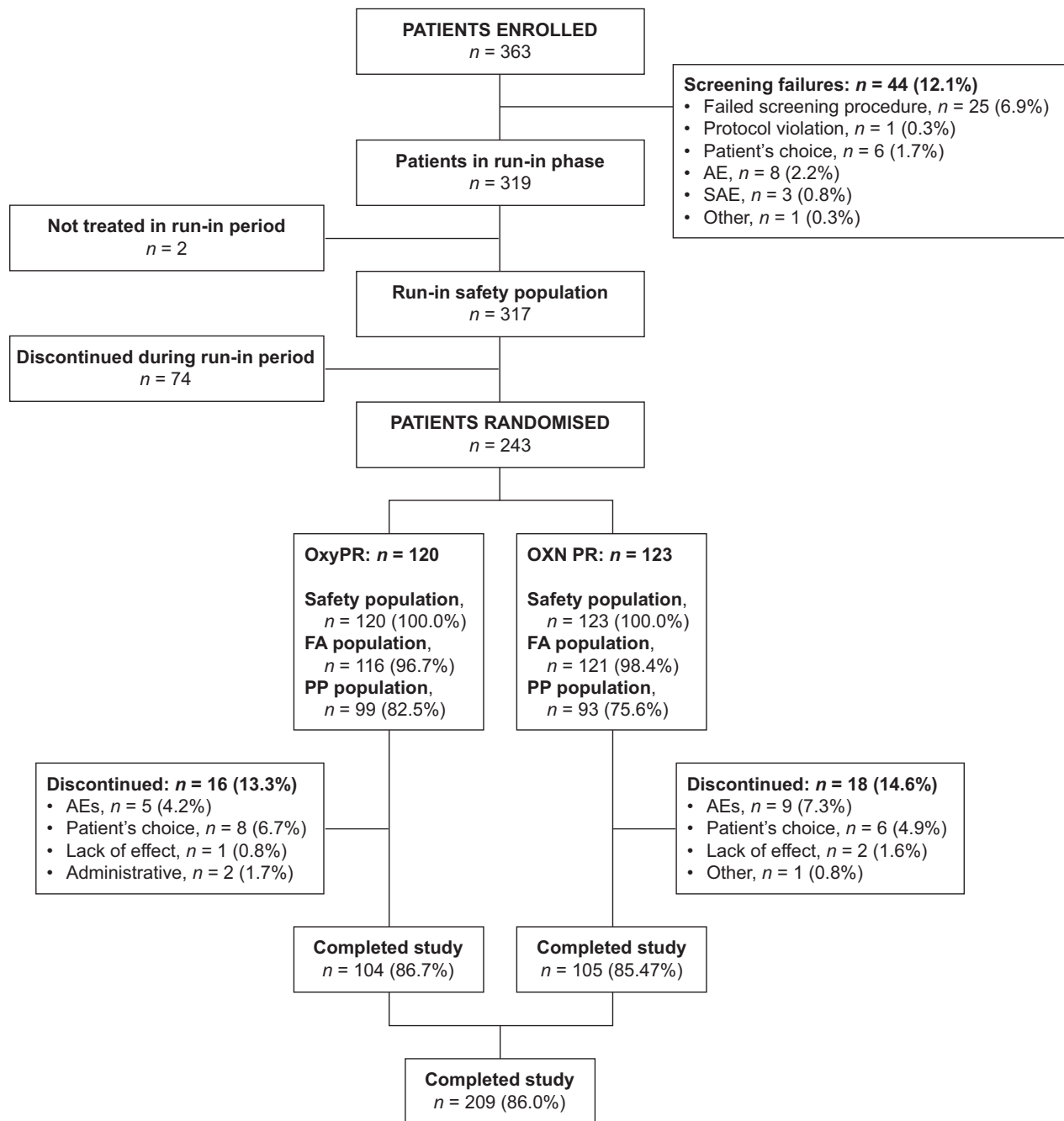
### 3.3 Efficacy outcomes

#### 3.3.1 Bowel function index

Change in mean BFI scores from baseline values during the 5 week study is shown in Fig. 3. Reductions in baseline scores were observed from Week 1 and were greater in the OXN PR group compared with the OxyPR group (−28.3 vs. −13.1). At Week 5, the mean change from baseline continued to be greater in the OXN PR group compared with the OxyPR group (−32.5 vs. −14.2). Based on the Mixed Model Repeated Measures Analysis (MMRM) the difference between the treatment groups was significant (LS mean difference (SE): −16.05 (3.14); *P* < 0.001, CI: −22.23, −9.86).

#### 3.3.2 Pain scores

Average 24-h pain scores remained stable in the range 3–4 in both treatment groups (Fig. 4) and non-inferiority of OXN PR to OxyPR was confirmed as statistically significant (*P* < 0.001). Subgroup analyses by dose level showed that subject receiving 100–120 mg oxycodone per day started with a mean pain score of 4.4 in the OXN PR group and 4.6 in the OxyPR group in the Run-in Phase (Table 4), which was almost 1 score lower than in patients receiving 140–160 mg/d, who had mean pain scores of 5.4 in the OXN PR group and 5.1 in the OxyPR group. However, pain scores at the beginning of the double-blind



**Figure 2** Consort flow diagram.

phase (baseline) and at Week 5 were comparable in the subgroups, which points to a greater level of pain relief in the higher dose subgroup.

### 3.3.3 Analgesic rescue medication

Analgesic rescue medication usage in the per protocol groups is shown in Table 5. Patients took an average of <1 dose and between 10 and 15 mg

OxyIR as analgesic rescue medication per day. No significant differences between treatment groups were detected for frequency of dosing ( $P = 0.5145$ ) or dose ( $P = 0.4328$ ) at Week 5.

### 3.3.4 Laxative rescue medication

Laxative rescue medication use in the full analysis population is shown in Table 5. Patients receiving



**Table 1** Baseline patient characteristics.

Characteristic	OXN PR (n = 123)	OxyPR (n = 120)
Age, mean (SD), range (years)	57.9 [11.03 (33–86)]	57.5 [12.33 (21–83)]
Gender, n (%)		
Male	53 (43.1)	47 (39.2)
Female	70 (56.9)	73 (60.8)
Weight, mean (SD), range (kg)	84.7 [21.45 (34–153)]	81.5 [20.67 (41–165)]
BMI, mean (SD), range (kg/m <sup>2</sup> )	29.2 [6.52 (14–47)]	28.3 [6.24 (17–50)]
Height, mean (SD), range (cm)	170.0 [9.97 (150–196)]	169.3 [9.80 (150–194)]

BMI, body mass index.

**Table 2** Concomitant medications according to therapeutic classification.

Therapeutic class	OXN PR (n = 123)	OxyPR (n = 120)
Alimentary tract and metabolism		
Acid-related disorders	46 (37.4)	41 (34.2)
Diabetes mellitus	19 (15.4)	12 (10.0)
Functional gastrointestinal disorders	7 (5.7)	6 (5.0)
Cardiovascular system		
Agents acting on the renin-angiotensin system	38 (30.9)	36 (30.0)
Beta blockers	28 (22.8)	24 (20.0)
Calcium channel blockers	16 (13.0)	16 (13.3)
Nervous system		
Analgesics	59 (48.0)	50 (41.7)
Other analgesics, antipyretics	55 (44.7)	48 (40.0)
Psychoanaleptics	54 (43.9)	45 (37.5)
Musculoskeletal system		
Non-steroidal anti-inflammatory agents, anti-rheumatic	37 (30.1)	28 (23.3)

**Table 3** Number of patients (%) at each dose level (full analysis population).

Dose level Oxycodone (mg) <sup>a</sup>	Total population		Cancer patients	
	OXN PR (n = 121)	OxyPR (n = 116)	OXN PR (n = 27)	OxyPR (n = 19)
100	40 (33.1)	42 (36.2)	6 (22.2)	5 (26.3)
120	26 (21.5)	30 (25.9)	7 (25.9)	5 (26.3)
140	15 (12.4)	13 (11.2)	3 (11.1)	3 (15.8)
160	31 (25.6)	28 (24.1)	9 (33.3)	4 (21.1)
Other <sup>b</sup>	9 (7.4)	3 (2.6)	2 (7.4)	2 (10.5)

<sup>a</sup>Dose level defined as the highest dose taken on more than seven consecutive days.

<sup>b</sup>No specific dose set for more than seven consecutive days.

OXN PR used significantly lower mean daily doses of laxative rescue medication at Week 5 compared with those receiving OxyPR; mean (SD) values were 0.6 (1.1) versus 1.2 (1.7) mg/day ( $P = 0.006$ ).

### 3.3.5. Complete spontaneous bowel movement

The mean number of CSBMs in the full analysis population increased to almost twice the baseline value in the OXN PR group in Week 1 (1.5–2.8) while in the OxyPR group a decrease was observed (2.1–1.5). The mean number of CSBMs remained stable through to Week 5 in the OXN PR group at 2.4 compared with 1.4 in the OxyPR group.

### 3.3.6 EuroQol EQ-5D-3L

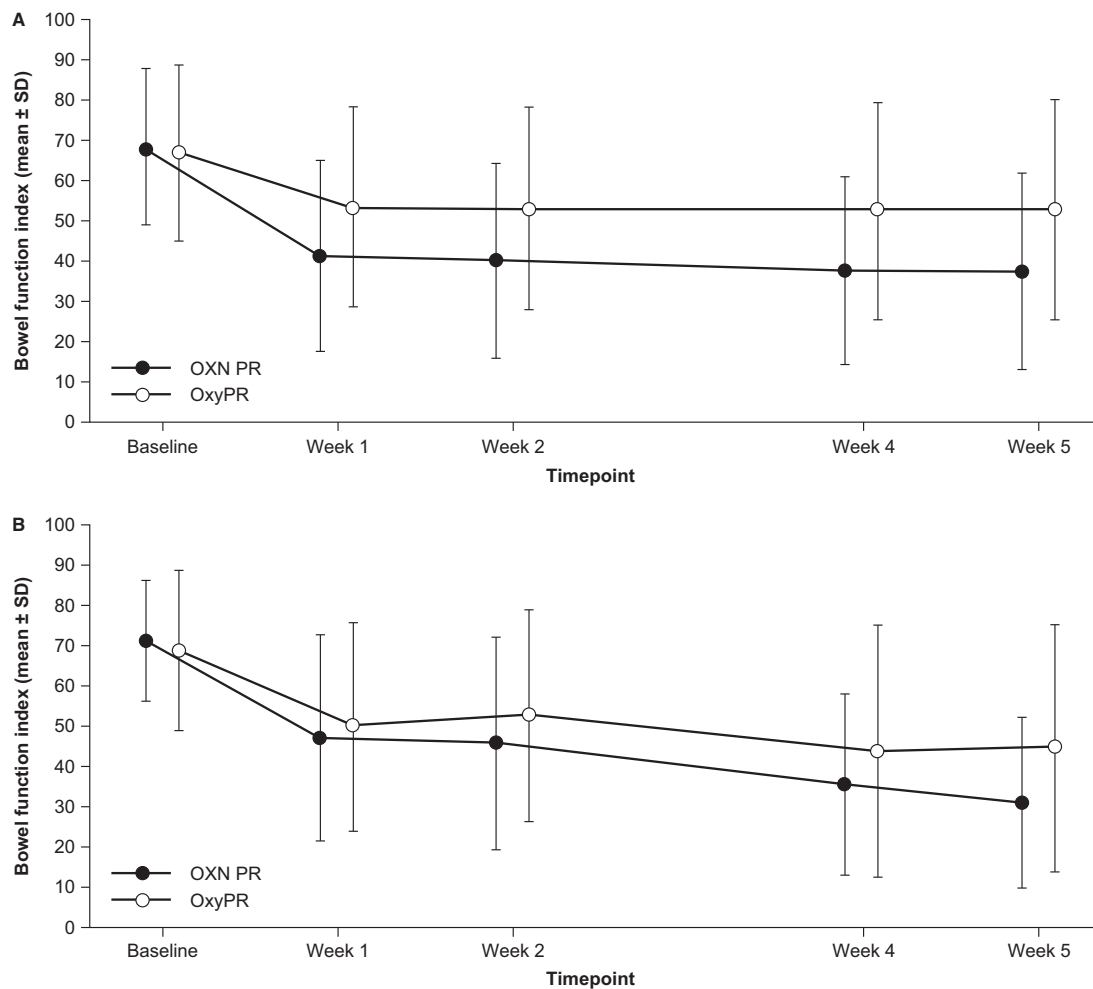
The overall EuroQol EQ-5D-3L scores were similar between the two treatment groups and showed a slight increase from Run-in to Week 5. The mean (SD) scores in the OXN PR groups were 0.48 (0.28) and 0.60 (0.25) at baseline and Week 5 respectively. These compare with the equivalent data of 0.45 (0.30) and 0.58 (0.27) for the OxyPR group.

### 3.4 Safety outcomes

Approximately 50% of patients experienced at least one AE in either group (Table 6). Adverse events with an incidence  $\geq 1\%$  incidence are shown in Table 7. The most common AE in either group was nausea. Four cancer patients died during the study from causes unrelated to the study medication. Nine patients in the OXN PR group and five patients in the OxyPR group discontinued due to AEs.

### 3.5 Cancer patient subanalysis

A total of 27 and 19 cancer patients were treated in the OXN PR and OxyPR groups. Dosages of analgesia administered were similar to those used in the overall population (Table 3). Primary endpoint data for BFI (Fig. 3) and pain scores (Fig. 4) reveal that a similar pattern to that shown for the total population. A MMRM analysis at Week 5 showed a clinically meaningful and statistically significant treatment difference in BFI of  $-14.0$  (8.1),  $P = 0.047$  in favour of OXN PR. Pain scores remained at a low level throughout the study and were comparable between groups. Rescue medication use is shown in Table 5. No significant differences between treatment groups were detected for frequency of analgesic rescue medication intake ( $P = 0.858$ ) or dose ( $P = 0.937$ ) throughout the study. Patients receiving



**Figure 3** Bowel Function Index in Full Analysis Populations: (A) total study group; and (B) cancer subgroups.

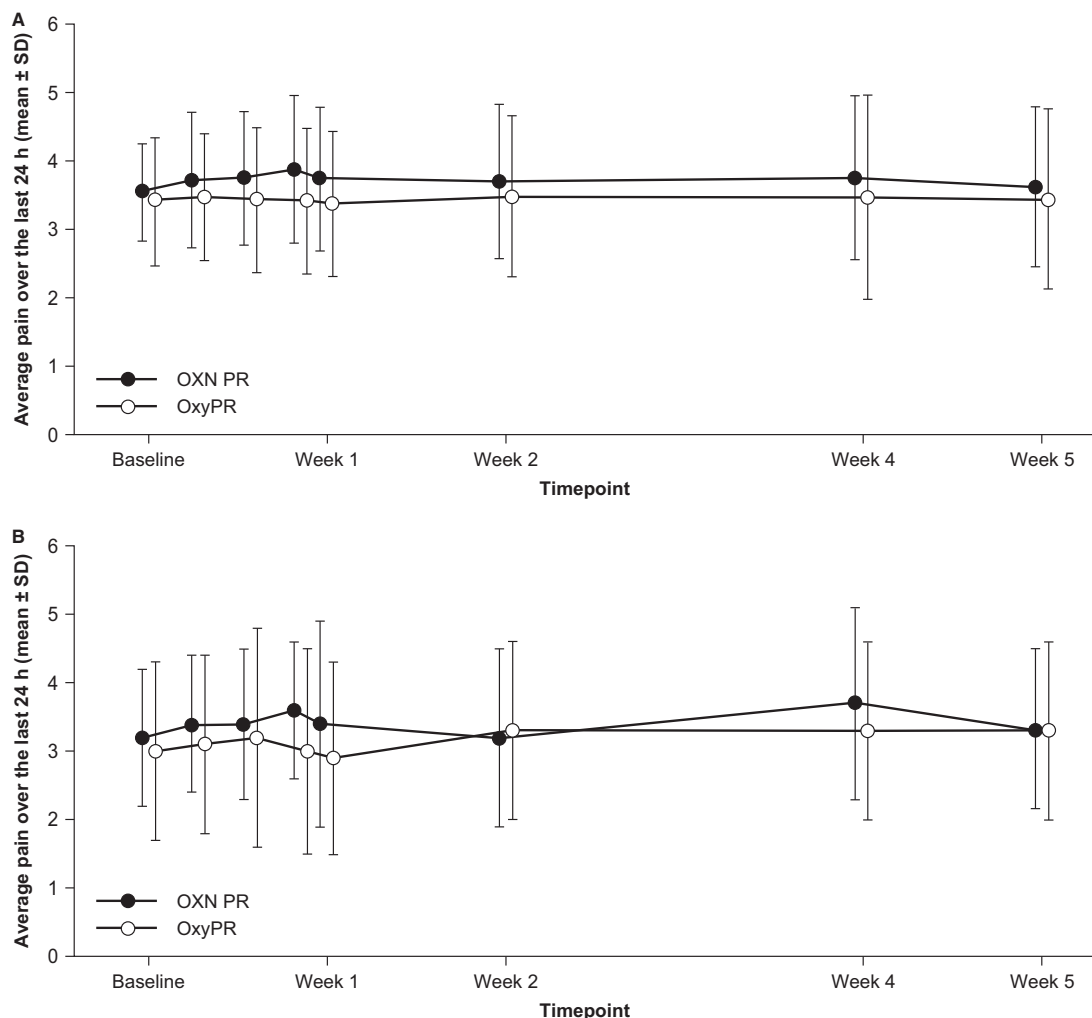
OXN PR used slightly lower mean daily doses of laxative rescue medication (0.8 mg) than those receiving OxyPR ( $P = 0.269$ ). Adverse events are shown in Table 7. Safety profile was as expected in a population with severe illnesses and a requirement for opioid analgesic treatment in the respective dose range.

#### 4. Discussion

This study demonstrated that OXN PR compared with OxyPR alone, significantly improves the bowel function of patients who require daily doses of opioids up to OXN PR 160/80 mg or the oxycodone equivalent. The reduction in BFI score at weeks 1 and 5 were greater in the OXN PR groups compared with OxyPR and the difference between groups was clinically relevant being >12 points (Rentz et al., 2009). Pain Intensity Scale daily scores based on clinic visits and daily diaries remained stable in both

treatment groups being in the range 3–4, which was considered mild; non-inferiority was demonstrated. In terms of analgesic rescue medication use with oxycodone, no significant difference was observed between the treatment groups. A number of Phase III, double-blind, randomised controlled clinical trials have been conducted comparing the analgesic efficacy and bowel function of OXN PR and OxyPR (Simpson et al., 2008; Vondrackowa et al., 2008; Löwenstein et al., 2009). Each of these studies showed that the improvement in bowel function was achieved through the addition of naloxone to the combination but without compromising the analgesic efficacy of the oxycodone component.

There was significantly less use of laxatives in terms of dose as well as frequency of intake in the OXN PR group. With regard to CSBM, an increase was observed as early as Week 1 in the OXN PR group and remained stable through to Week 5.



**Figure 4** Pain scores: (A) total study group; and (B) cancer subgroups.

**Table 4** Subanalysis of pain score according to dose of OXN PR or OxyPR received.

	OXN PR		OxyPR	
	100–200 mg/day Oxycodone (n = 60)	140–160 mg/day Oxycodone (n = 33)	100–200 mg/day Oxycodone (n = 64)	140–160 mg/day Oxycodone (n = 35)
Time point				
Run-in (n)	59	33	63	35
Mean (SD)	4.4 (1.8)	5.4 (1.6)	4.6 (1.9)	5.1 (1.8)
Median (range)	4.0 (1–10)	5.0 (2–10)	4.0 (0–8)	5.0 (2–9)
Baseline (n)	60	33	64	35
Mean (SD)	3.5 (0.79)	3.7 (0.53)	3.3 (1.03)	3.5 (0.78)
Median (range)	4.0 (1–5)	4.0 (2–4)	4.0 (1–6)	4.0 (1–4)
Week 5 (n)	60	33	62	32
Mean (SD)	3.6 (1.29)	3.6 (0.94)	3.4 (1.40)	3.5 (1.19)
Median (range)	4.0 (0–6)	4.0 (1–6)	4.0 (0–7)	4.0 (1–6)
Change from baseline (n)	60	33	62	32
Mean (SD)	0.2 (1.32)	–0.1 (0.70)	0.0 (1.34)	0.1 (0.84)
Median (range)	0.0 (–4 to 4)	0.0 (–1 to 2)	0.0 (–4 to 4)	0.0 (–3 to 2)



**Table 5** Analgesic and laxative rescue medication use in the per protocol population study groups for the overall study populations and the cancer subgroup patients.

Time point	Overall population		Cancer patients	
	OXN PR	OxyPR	OXN PR	OxyPR
Analgesic rescue medication, mg/day <sup>a</sup>				
Baseline (n)	93	99	17	14
Mean (SD)	11.8 (14.7)	11.6 (15.7)	15.1 (19.7)	11.9 (15.2)
Median (range)	6.4 (0–59)	4.6 (0–79)	7.1 (0–59)	4.5 (0–46)
Week 5 (n)	93	99	17	14
Mean (SD)	13.8 (16.4)	14.5 (18.8)	16.5 (18.3)	15.2 (17.4)
Median (range)	6.7 (0–68)	3.0 (0–74)	14.3 (0–58)	11.1 (0–50)
Laxative rescue medication, mg/day <sup>b</sup>				
Baseline (n)	121	116	27	19
Mean (SD)	1.8 (1.5)	1.5 (1.7)	1.5 (1.3)	2.5 (1.7)
Median (range)	1.4 (0–7)	1.1 (0–9)	1.4 (0–4)	2.5 (0–6)
Week 5 (n)	106	106	21	15
Mean (SD)	0.6 (1.1)	1.2 (1.7)	0.6 (1.1)	1.5 (2.3)
Median (range)	0.0 (0–5)	(0–7)	0.0 (0–4)	0.0 (0–6)

<sup>a</sup>PP population. Time points are relative to randomisation.

<sup>b</sup>FA population. Time points are relative to first intake of Double-blind IMP.

**Table 6** Overall summary of adverse events (AEs), safety population.

	Overall population		Cancer patients	
	OXN PR (n = 123)	OxyPR (n = 120)	OXN PR (n = 28)	OxyPR (n = 22)
No. AEs	185	143	46	52
Patients with ≥1 AE, n (%)	67 (54.5)	57 (47.5)	18 (64.3)	15 (68.2)
Patients with ≥1 treatment-related <sup>a</sup> AE, n (%)	47 (38.2)	29 (24.2)	7 (25.0)	5 (22.7)
No. severe AEs	10	14	4	9
Patients with ≥1 severe AE, n (%)	10 (8.1)	9 (7.5)	4 (14.3)	5 (22.7)
Patients with ≥1 treatment-related <sup>a</sup> severe AE, n (%)	8 (6.5)	5 (4.2)	2 (7.1)	2 (9.1)
Number of SAE	3	6	3	5
Patients with ≥1 SAE, n (%)	3 (2.4)	4 (3.3)	3 (10.7)	3 (13.6)
Patients with ≥1 treatment-related <sup>a</sup> SAE, n (%)	0	0	0	0
Patients who died	1 (0.8)	3 (2.5)	1 (3.6)	3 (13.6)

SAE, serious adverse event.

Data are n (%) unless stated otherwise.

<sup>a</sup>Investigator considered the AE to be 'unlikely', 'possibly', 'probably' or 'definitely' related to study medication.

There was a decrease in mean CSBM in the OxyPR group at Week 1 through to Week 5 compared with an increase in the OXN PR group of 1.3 at Week 1 and 0.9 at Week 5. An increase in CSBM of 1 is

**Table 7** Most frequent adverse events (AEs) occurring with an incidence of ≥ 1% (safety population).

	Overall population		Cancer patients	
	OXN PR (n = 123)	OxyPR (n = 120)	OXN PR (n = 28)	OxyPR (n = 22)
Most frequent AEs overall population, n (%)				
Nausea	12 (9.8)	6 (5.0)	1 (3.6)	2 (9.1)
Hyperhidrosis	8 (6.5)	3 (2.5)	2 (7.1)	0
Diarrhoea	6 (4.9)	5 (4.2)	0	0
Upper abdominal pain	4 (3.3)	4 (3.3)	0	0
Drug withdrawal syndrome	4 (3.3)	1 (0.8)	0	0
Restlessness	5 (4.1)	1 (0.8)	0	0
Dizziness	4 (3.3)	1 (0.8)	0	1 (4.5)
Most frequent AEs cancer patients, n (%)				
Sinus tachycardia	0	2 (1.7)	0	2 (9.1)
Gastritis	2 (1.6)	0	2 (7.1)	0
Blood albumin decreased	0	2 (1.7)	0	2 (9.1)
Blood calcium decreased	0	3 (2.5)	0	2 (9.1)
Hypercholesterolaemia	3 (2.4)	0	2 (7.1)	0
Hypertriglyceridaemia	2 (1.6)	0	2 (7.1)	0
Hyponatraemia	1 (0.8)	3 (2.5)	1 (3.6)	2 (9.1)
Neoplasm malignant	2 (1.6)	3 (2.5)	2 (7.1)	3 (13.6)
Tremor	4 (3.3)	3 (2.5)	2 (7.1)	1 (4.5)
Anxiety	1 (0.8)	5 (4.2)	0	2 (9.1)

Data are n (%) unless stated otherwise.

considered clinically relevant. The findings with the EuroQol EQ-5D-3L showed that the addition of naloxone did not change the improved health state that can be gained using oxycodone for relief of severe pain. The improved bowel function in the OXN

PR group supports not only the benefits of naloxone in the combination but also that oxycodone rescue medication can be used in addition to OXN PR without reducing this benefit.

The control of pain experienced by cancer is difficult to achieve over the time course required. Constipation can greatly impact on a patient's quality of life and certainly in those patients with cancer whose quality is already affected by the disease itself. One study reported that, constipation was considered by cancer patients to cause greater discomfort than the actual pain they were experiencing (Abramowitz et al., 2013). The subanalysis of the study evaluating outcome in cancer patients revealed that the bowel function and analgesic benefits achieved were comparable to those in the population as a whole. No additional safety concerns were identified in this subgroup.

In summary, this study provides confirmatory evidence that treatment with oxycodone/naloxone in daily doses of up to 160/80 mg, compared with oxycodone alone, significantly improves the bowel function of patients who require oxycodone equivalent daily doses up to OXN PR 160/80 mg, while still providing comparable analgesic efficacy. Outcome in cancer patients, a difficult to treat group, is comparable to the total population. An important consequence of improvement in bowel function is that patients may find the long-term use of opioid treatment for chronic pain more acceptable. A long-term open-label extension phase study involving doses of OXN PR up to 180/90 mg will be reported separately.

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### Author contributions

A. Ellery: Investigator in this study, interpretation of the data, critical revision of the manuscript, review and final approval of the version to be published. D. Dupouiron: Investigator in this study, interpretation of the data, critical revision of the manuscript, review and final approval of the version to be published. O. Loewenstein: Investigator in this study, interpretation of the data, critical revision of

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### References

- Abramowitz, L., Béziaud, N., Labreze, L., Giardina, V., Caussé, C., Chuberre, B., Allaert, F.A., Perrot, S. (2013). Prevalence and impact of constipation and bowel dysfunction induced by strong opioids: A cross-sectional survey of 520 patients with cancer pain: DYONISOS study. *J Med Econ* 16, 1423–1433.
- Cherny, N., Ripamonti, C., Pereira, J., Davis, C., Fallon, M. et al. (2001). Strategies to manage the adverse effects of oral morphine: An evidence-based report. *J Clin Oncol* 19, 2542–2554.
- De Schepper, H.U., Cremonini, F., Park, M.I., Camilleri, M. (2004). Opioids and the gut: Pharmacology and current clinical experience. *Neurogastroenterol Motil* 16, 383–394.
- Fishman, J., Roffwarg, H., Hellman, L. (1973). Disposition of naloxone-7,8-3H in normal and narcotic dependent men. *J Pharmacol Exp Ther* 187, 575–580.
- Linn, A.J., Steinbrook, R.A. (2007). Peripherally restricted mu-opioid receptor antagonists: A review. *Tech Reg Anesth Pain Manage* 11, 27–32.
- Löwenstein, O., Leyendecker, P., Hopp, M., Schutter, U., Rogers, P.D. et al. (2009). Combined prolonged-release oxycodone and naloxone improves bowel function in patients receiving opioids for moderate-to-severe non-malignant chronic pain: A randomised controlled trial. *Expert Opin Pharmacother* 10, 531–543.
- Meissner, W., Schmidt, U., Hartmann, M., Kath, R., Reinhart, K. (2000). Oral naloxone reverses opioid-associated constipation. *Pain* 84, 105–109.
- Meissner, W., Leyendecker, P., Mueller-Lissner, S., Nadstawek, J., Hopp, M. et al. (2009). A randomised controlled trial with prolonged-release oral oxycodone and naloxone to prevent and reverse opioid-induced constipation. *Eur J Pain* 13, 56–64.
- Rentz, A.M., Yu, R., Müller-Lissner, S., Leyendecker, P. (2009). Validation of the Bowel Function Index to detect clinically meaningful changes in opioid-induced constipation. *J Med Econ* 12, 371–383.
- Simpson, K., Leyendecker, P., Hopp, M., Müller-Lissner, S., Löwenstein, O. et al. (2008). Fixed-ratio combination oxycodone/naloxone compared with oxycodone alone for the relief of opioid-induced constipation in moderate to-severe noncancer pain. *Curr Med Res Opin* 24, 3503–3512.
- Vondrackowa, D., Leyendecker, P., Meissner, W., Hopp, M., Szombati, I. et al. (2008). Analgesic efficacy and safety of oxycodone in combination with naloxone as prolonged-release tablets in patients with moderate to severe chronic pain. *J Pain* 9, 1144–1154.