EJP
European Journal of Pain

ORIGINAL ARTICLE

Long-term efficacy and safety of oxycodone-naloxone prolonged-release formulation (up to 180/90 mg daily) – results of the open-label extension phase of a phase III multicenter, multiple-dose, randomized, controlled study

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Funding sources
Mundipharma Research GmbH & Co. KG., Limburg, Germany funded the study as well as the writing and editorial assistance for this manuscript (provided by Dr. Christine McKillop of MedSciMedia Ltd., Cambridgeshire, UK). W. Kremers, B. Bosse and M. Hopp are employees of Mundipharma Research GmbH & Co. KG.

Conflicts of interest
D. Dupoiron: 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, Gruenenthal, Servier. He was contributor in seminars and workshops for Mundipharma, Gruenenthal, 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.

Accepted for publication
15 March 2017

doi:10.1002/ejp.1050

Abstract

Background: The inclusion of naloxone with oxycodone in a fixed combination prolonged-release formulation (OXN PR) improves bowel function compared with oxycodone (Oxy) alone without compromising analgesic efficacy. In a recent 5-week, randomized, double-blind comparative trial of OXN PR and OxyPR, it could be shown that the beneficial properties of OXN PR extend to doses up to 160/80 mg.
Methods: Bowel function, pain, quality of life (QoL) and safety of OXN PR up to 180/90 mg daily were evaluated in a 24-week open-label extension phase of the 5-week randomized comparative study in patients with non-malignant or malignant pain requiring opioids and suffering from opioid-induced constipation.
Results: During treatment with a mean (SD) daily dose OXN PR of 130.7 (26.56) mg (median, maximum: 120 and 180 mg), the Bowel Function Index (BFI) decreased from 45.3 (26.37) to 26.7 (21.37) with the largest decrease seen in the first week. The average pain over the last 24 h remained stable (median Pain Intensity Scale score 4.0) and QoL was maintained throughout the study. Adverse events were consistent with the known effects of OXN PR and no new safety concerns emerged. Equivalent efficacy and safety benefits were observed in cancer patients.
Conclusions: The OXN PR in doses up to 180/90 mg provides effective analgesia with maintenance of bowel function during long-term treatment. The beneficial effects of such dose levels of OXN PR contribute to stable patient-reported QoL and health status despite serious underlying pain conditions, such as cancer.
Significance: In patients with pain requiring continuous opioid therapy at doses above 80 mg of oxycodone, stable and effective long-term analgesia can be achieved using OXN PR up to 180/90 mg daily without compromising bowel function and may be preferential to supplemental oxycodone.

1. Introduction

During the past 20 years, a prolonged-release formulation of the semi-synthetic opioid analgesic oxycodone (OxyPR) has been widely used for the treatment of moderate-to-severe cancer and non-cancer pain requiring around-the-clock opioid analgesia. While such strong opioids have proven analgesic efficacy in the management of pain of different aetiologies, they produce a variety of treatment-related side-effects, the most common of which is opioid-induced bowel dysfunction (OIBD) (Pappagallo, 2001; Panchal et al., 2007; Leppert, 2015). The symptoms of OIBD, particularly constipation, can significantly affect patients' quality of life and lead to undertreatment of pain as a consequence of reduced compliance with opioid therapy (Fishman et al., 1973; Pappagallo, 2001; Panchal et al., 2007; Leppert, 2015).

Naloxone is a competitive antagonist of opioid receptors able to reverse opioid-mediated effects. When administered orally, the systemic bioavailability of naloxone is <2% (Fishman et al., 1973), which results in selective antagonism of intestinal opioid receptors (Choi and Billings, 2002). Co-administration of oral naloxone can thus improve the symptoms of OIBD (Meissner et al., 2000). This targeted opioid receptor antagonism underpins the rationale for a prolonged-release formulation containing oxycodone and naloxone in a 2:1 ratio (OXN PR). Clinical studies have demonstrated that OXN PR provides effective analgesia without the predictable gastrointestinal effects of oxycodone monotherapy (Simpson et al., 2008; Vondrackowa et al., 2008; Löwenstein et al., 2009; Meissner et al., 2009; Reimer et al., 2009; Ahmedzai et al., 2012), and this effect is maintained during long-term treatment (Blagden et al., 2014; Ahmedzai et al., 2015).

The OXN PR is currently available across Europe in four dose strengths for twice daily use: OXN5/2.5 mg, OXN10/5 mg, OXN20/10 mg and OXN40/20 mg. The maximum daily dose currently approved in Europe is 160/80 mg OXN PR. The indication for the drug is "'severe pain' which can be adequately managed only with opioid analgesics. The opioid antagonist naloxone is added to counteract opioid-induced constipation by blocking the action of oxycodone on opioid receptors locally in the gut." Clinical experience and occasional reports suggest there is a need for doses higher than the previously approved daily dose at the time of OXN PR 80/40 mg (Ahmedzai et al., 2012; Bujedo, 2015); patients taking OXN PR who require further pain relief are allowed to take supplemental OxyPR up to 400 mg. In consequence, the safety and efficacy of OXN PR and OxyPR in equivalent daily doses of up to 160 mg OxyPR was established in a randomized, double-blind, controlled trial. The results of the 5-week double-blind phase of the study demonstrated that OXN PR up to a dose of 160/80 mg per day was effective and generally well-tolerated (Dupoiron et al., 2017). Here, data with respect to bowel function, pain and safety parameters during a 24-week open-label extension of the trial are presented.

2. Methods

2.1 Study design

This extension study follows a preceding randomized, double-blind, multicentre study designed to confirm improvement in bowel function and non-inferiority in analgesic efficacy of OXN PR in daily doses up to 160/80 mg compared with OxyPR alone in patients with non-malignant or malignant pain requiring opioids (ClinicalTrials.gov identifier NCT 01438567). The extension phase consisted of an additional 24 weeks of treatment with open-label OXN PR up to a maximum daily dose of 180/90 mg, with the objective of assessing bowel function, pain and safety of OXN PR during long-term use. An additional follow-up assessment of adverse events was performed 7 days after the end of the study or at early discontinuation.

2.2 Patients and treatments

Patients who completed the preceding 5-week double-blind study phase or discontinued prematurely from the double-blind phase due to constipation were eligible for this study. Entrance to the study also required patients needing continuation of daily opioid analgesic treatment who were likely to benefit from chronic opioid therapy for the duration of the study. Further inclusion and exclusion criteria were applied at screening, before the double-blind study phase and are reported in more detail elsewhere (Dupoiron et al., 2016). Patients included had 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.

All patients who entered the extension phase started with the oxycodone PR dose (as OXN PR or OxyPR) that they were receiving at the end of the

double-blind phase or, if applicable, at early discontinuation. The different daily dose levels were OXN PR 100/50 mg, OXN PR 120/60 mg, OXN PR 140/70 mg or OXN PR 160/80 mg. OXN PR or OxyPR was switched to open-label OXN PR in a stepwise, double-blind, double-dummy manner during the first week of the extension phase. Oxycodone immediate-release (OxyIR) could be administered not sooner than every 4 h to a maximum of six rescue doses per day. If a patient needed more than two OxyIR doses per day for analgesic rescue, the OXN PR dose could be increased. From the end of the first week onwards, titration up to the maximum daily dose of OXN PR 180/90 mg was permitted. Rescue medication for analgesia and laxation could be prescribed as needed. During the first week of the study, however, OxyIR for breakthrough pain and bisacodyl 5 or 10 mg/day for constipation were the only permitted rescue medications. Concomitant medications after the first week could include other opioid analgesics and laxatives other than bisacodyl.

2.3 Efficacy assessments

2.3.1 Bowel Function Index

The Bowel Function Index (BFI) is a validated 3-item questionnaire specifically developed to assess three key characteristics of opioid-induced constipation from the patient's perspective: ease of defaecation, feeling of incomplete bowel evacuation and his or her personal judgement of constipation (Ducrotté and Caussé, 2012). A BFI reference range for non-constipated chronic pain patients can be defined as 0–28.8 and covers the vast majority of non-constipated patients (Überall et al., 2011). At each clinic visit (baseline, Weeks 1, 2, 4 and every 4 weeks until the end of the study), patients subjectively rated each item according to their experience of the previous week using a numerical rating scale (NRS) of 0–100 in which 0 = no symptoms and 100 = most severe symptoms. The BFI score was calculated as the mean of the three component item scores.

2.3.2 Average pain over the last 24 h

Analgesic efficacy was measured as 'Average pain over the last 24 h' based on the Pain Intensity Scale, an NRS of 0–10 (0 = no pain and 10 = worst imaginable pain), which was assessed at each visit (baseline, Weeks 1, 2, 4 and then every 4 weeks until the end of the study) and in daily diaries.

2.3.3 EuroQol EQ-5D-3L

The EQ-5D-3L self-reported 5-dimension (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) questionnaire and EQ 'health today' visual analogue scale (VAS) responses were recorded at Weeks 1, 12 and 24. The responses to the five dimensions of the EQ-5D-3L were also converted into an overall EQ-5D-3L summary index.

2.4 Safety assessments

Safety was assessed using adverse event (AE) monitoring. The safety parameters used in this study include an evaluation of opioid withdrawal as assessed by the Modified Subjective Opiate Withdrawal Scale (SOWS; Handelsman et al., 1987) and the Clinic Opiate Withdrawal (COWS; Wesson and Ling, 2003) questionnaires. Treatment was discontinued if the modified SOWS score was >26 or the COWS score was >24.

2.4.1 AEs

Adverse events noted from spontaneous reports in patient interviews were recorded at baseline, Weeks 1, 2, 4 and then every 4 weeks until the end of the study. Severity and relationship with study medication was assessed. Clinically significant abnormal laboratory test values, which required intervention or were judged by the investigator to be out of range relative to the patient's medical profile, were recorded as AEs. Important untoward medical events or reactions that resulted in death or hospitalization were potentially life-threatening or otherwise jeopardized a patient, or required intervention to prevent such a detrimental clinical course were considered serious AEs (SAEs).

2.4.2 Evaluation of opioid withdrawal

Signs and symptoms of opioid withdrawal were evaluated at Week 1 by the physician-administered COWS and the patient-reported modified SOWS; the modified SOWS excludes the SOWS item number 16, 'I feel like shooting up today', since it did not apply to the patients in this study.

2.4.3 Other safety assessments

Safety assessments also included monitoring clinical laboratory test results, vital sign measurements, physical examination, electrocardiogram (ECG) recording, concomitant medication use and patients' reason(s) for discontinuation.

2.5 Statistical analysis

Analyses were completed on total exposure safety population, defined as those patients who received at least one dose of OXN PR in the extension phase and had at least one safety assessment after the first dose of extension phase study medication. A subgroup of cancer patients with ongoing malignancies at start of the study were analysed for BFI, pain and EQ-5D-3L in the same way as the total patient population.

The BFI score and 'Average pain over the last 24 h' each week and change from baseline at each week were summarized using descriptive statistics for the overall study population, according to the study medication that the patients received during the double-blind study phase of the study (OXN PR or OxyPR), and for the subgroup of cancer patients. Each of the three BFI items was also summarized. The EQ-5D-3L dimension scores, including the summary index, and the EQ 'health today' VAS score were summarized by week using descriptive statistics. Data were also cross-tabulated with frequency and percent for all possible scores.

All safety variables were summarized by week where appropriate. Continuous variables were reported using descriptive statistics and categorical variables summarized by number and percentage of patients in each category. AEs were classified into standardized medical terminology from the verbatim description (Investigator term) using MedDRA (version 14.0).

3. Results

3.1 Patients

Of the 209 patients who completed the preceding double-blind study phase, 195 patients enrolled in the extension phase and all received at least one dose of OXN PR (Fig. 1). No discontinuations occurred due to constipation. The most common AE resulting in discontinuation was diarrhoea in three patients. The total exposure safety population comprised 80 male and 115 female patients with a mean age of 57.1 years (Table 1). Approximately three-quarters of patients had pain attributable to musculoskeletal and connective tissue disorders, such as back pain, spinal osteoarthritis, arthritis and intervertebral disc protrusion.

3.2 Treatment exposure

The distribution of different mean dose levels of oxycodone was across the full dose range available, in that 26.7% of patients received a mean dose level of ≤100 mg and 12.8% received a dose of >160 to ≤180 mg (Table 2). The mean exposure to OXN PR was 154.1 days with a maximum exposure of 194 days. The mean (SD) daily dose of oxycodone was 130.7 (26.6) mg and the median (range) was 120 (89–180) mg.

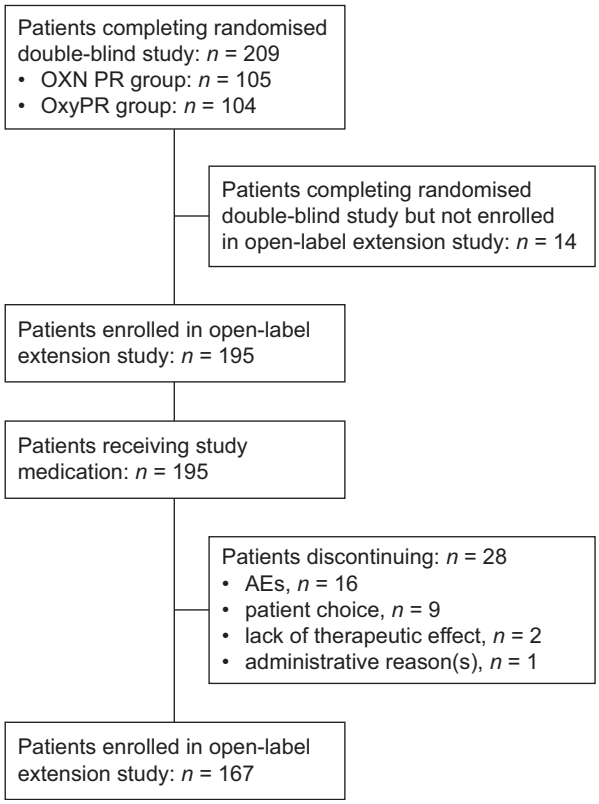


Figure 1 Study disposition.

3.3 Efficacy

3.3.1 Bowel Function Index

The BFI decreased during the study (Fig. 2) with the largest decrease seen in the first week, during which the mean (SD) BFI decreased from 45.3 (26.37) to 30.8 (23.02). The mean (SD) BFI at the end of the study was 26.7 (21.37). Patients who had received OxyPR during the preceding double-blind phase started this extension phase with a higher BFI than those who had received OXN PR; 53.6 (25.40) versus 37.5 (24.95) (Fig. 3). In the group previously treated with OxyPR, the BFI decreased to 23.7 (19.00) by the end of the study and to 29.5 (23.12) in patients who received OXN PR during the double-blind phase.

Table 1 Patient characteristics: total exposure safety population.

Characteristic	OXN PR (n = 195)
Age, mean (SD), range (years)	57.1 (11.39 [21–86])
Gender (%)	
Male	80 (41.0)
Female	115 (59.0)
Weight, mean (SD), range (kg)	83.5 (20.92 [34–160])
BMI, mean (SD), range (kg/m^2)	28.8 (6.26 [14–49])
Height, mean (SD), range (cm)	169.9 (9.84 [150–196])
Pain-causing condition	
Back pain	104 (53.1)
Spinal disorders	84 (43.1)
Osteoarthritis	27 (14.0)
Arthralgia	13 (6.60
Neuralgia	27 (14.0)
Malignancy	35 (17.9)
Breast cancer	13
Lung cancer	7
Metastatic (bone, lung, lymph nodes)	21
Hypertension	77 (39.5)
Depression	46 (23.5))
Hypercholesterolaemia	29 (14.8)
Obesity	22 (11.5)
Menopausal or postmenopausal	21 (10.7)
Insomnia	18 (9.1)
Type 2 diabetes mellitus	14 (7.0)
Dyspepsia	13 (6.6)
Post laminectomy syndrome	13 (6.6)
Myocardial ischaemia	10 (5.3)
Pain	10 (5.3)

BMI, body mass index.
Data are n (%) unless stated otherwise.

Table 2 Oxycodone daily dose levels after Week 1 in the total exposure safety population and cancer patient subgroup.

Dose level (mg)	Total (n = 195)	Cancer patients (n = 35)
≤100	52 (26.7)	7 (20.0)
>100 to ≤120	48 (24.6)	8 (22.9)
>120 to ≤140	23 (11.8)	7 (20.0)
>140 to ≤160	47 (24.1)	6 (17.1)
>160 to ≤180	25 (12.8)	7 (20.0)

Data shown are n (%).

The pattern of change in BFI was similar in patient subgroups. Changes in individual parameters of the BFI were also consistent with the pattern of change in the whole BFI.

3.3.2 Average pain over the last 24 h

The average pain over the last 24 h remained stable over the 24-week study in both groups, that is, in patients who had received OxyPR in the double-blind phase as well as patients who remained on OXN PR (Fig. 4). The median pain score was 4.0 throughout the study, in patients who had received OxyPR in the double-blind phase as well as patients who remained on OXN PR. There were no differences observed between subgroups of younger, older, male and female patients, or between different dose levels of OXN PR (Table 3). The overall mean pain score over 24 h was 3.6 at baseline, and

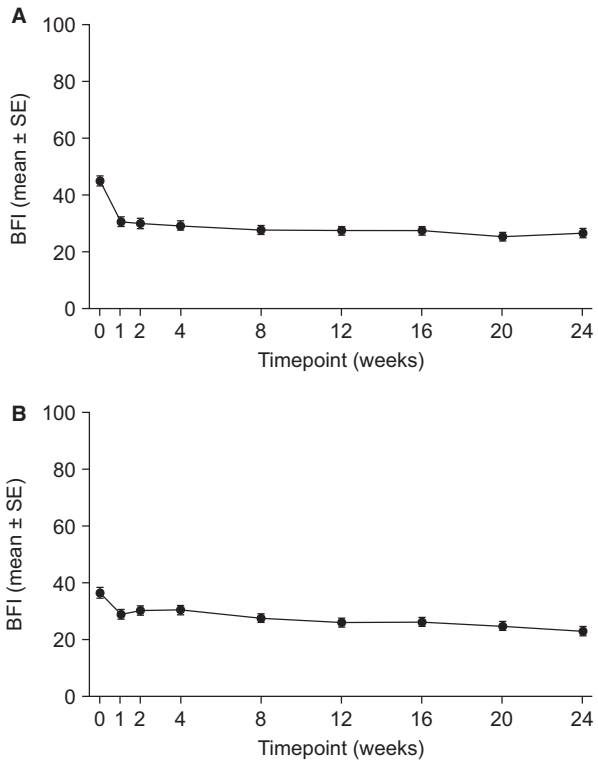


Figure 2 Bowel Function Index (BFI) during the study; observed values in (A) the total exposure safety population and (B) cancer patients.

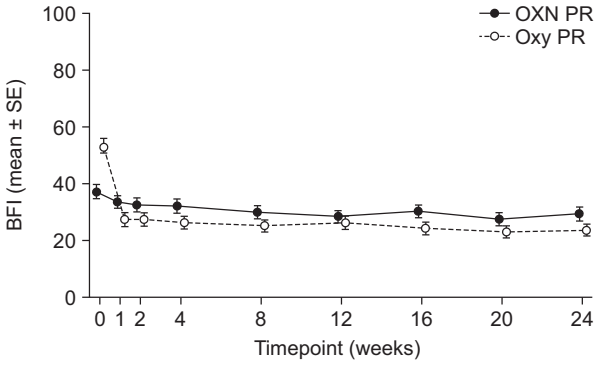
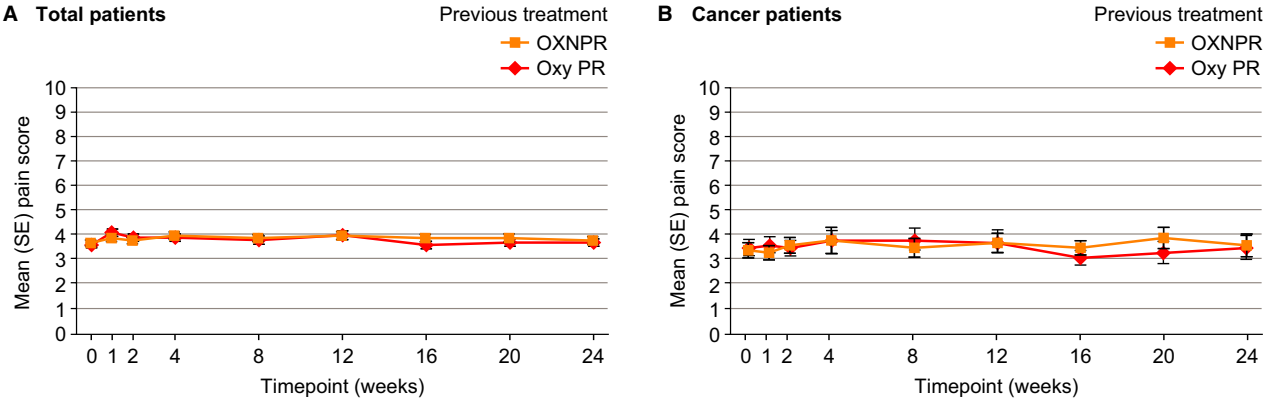


Figure 3 Bowel Function Index (BFI) during study; observed values in the total exposure safety population according to treatment with OXN PR or OxyPR in the preceding double-blind study.



Patient numbers:

Time	0	1	2	4	8	12	16	20	24
Total OXNPR	100	100	96	96	96	94	90	89	85
Total Oxy	94	92	89	89	86	83	82	81	78
Cancer OXNPR	22	22	21	19	19	19	17	16	14
Cancer Oxy	13	13	13	13	12	12	11	11	11

Figure 4 Mean (SE) pain over the last 24 h assessed by Pain Intensity Scale during the study in the total exposure safety population and in the cancer patient subgroup. Results shown according to the medication applied during the previous double-blind study, that is, OxyPR or OXN PR.

Table 3 Average pain over last 24 h assessed by Pain Intensity Scale according to dose level in the total exposure safety population.

Week	Total 100–120 mg (n = 97)	Total 140–160 mg (n = 68)	Total >160 mg (n = 24)
0	3.6 (1.11); 4.0 [0–6] (n = 96)	3.7 (1.16); 4.0 [1–7] (n = 68)	3.9 (1.03); 4.0 [1–6] (n = 24)
1	3.9 (1.44); 4.0 [0–9] (n = 97)	3.9 (1.39); 4.0 [1–8] (n = 68)	4.5 (1.41); 4.0 [1–7] (n = 24)
24	3.7 (1.17); 4.0 [1–7] (n = 84)	3.9 (1.45); 4.0 [1–8] (n = 61)	4.4 (1.85); 4.0 [1–10] (n = 18)

Data are mean (SD); median [range].

remained between 3.8 and 4.0 throughout the study.

3.3.3 EuroQoL EQ-5D-3L

The EuroQoL EQ-5D-3L index changed little during the 24-week study (Table 4). In the dimensions scores, there was a trend of decrease in each score through the study. This trend occurred in the all dimensions except in the 'Usual activities', where the number of patients who were unable to perform their daily tasks increased from 6 in Week 1 to 9 in Week 24. Patients' assessment of their general health status also remained stable throughout the study.

Table 4 EuroQoL EQ-5D-3L index at Weeks 1, 12 and 24 in the total exposure safety population and the cancer patient subgroup.

Week	Total (n = 195)	Cancer patients (n = 35)
1	0.59 (0.25); 0.6 [0–1] (n = 191)	0.57 (0.23); 0.6 [0–1] (n = 35)
12	0.60 (0.23); 0.6 [0–1] (n = 176)	0.55 (0.28); 0.6 [0–1] (n = 31)
24	0.59 (0.23); 0.6 [0–1] (n = 164)	0.56 (0.26); 0.6 [0–1] (n = 25)

Data are mean (SD); median [range].

3.3.4 Concomitant medication

Nearly all patients (97.9%) were taking at least one concomitant medication. The most frequently used drug class within the alimentary tract and metabolism medications were drugs for acid related disorders, which were taken by 77 (39.5%) patients. Drugs used in diabetes were used by 25 (12.8%) patients, and drugs for functional gastrointestinal disorders were used by 14 (7.2%) patients. In the first week, during which laxatives were supplied as rescue medication, five patients (2.6%) took laxatives as needed and two patients (1.0%) took laxatives regularly. After the first week, when laxatives had to be prescribed, only 26 patients (13.3%) took them regularly.

Medications for nervous system disorders were used by 172 patients (88.2%), most of whom took

analgesics (77.9%), including opioids (47.2%). These opioids were primarily taken as rescue medication on an 'as needed' basis. Of the 92 patients who took opioids, 74 took either a medical product which was immediate release or the use was described 'as required' in the reported name of therapy, or did not receive a regular daily dose, or received the medication for a limited time only.

3.4 Safety

3.4.1 AEs

A total of 128 patients (65.6%) had 452 AEs and 21 patients (10.8%) experienced 36 SAEs (Table 5). The majority of AEs were mild or moderate in severity, and severe AEs occurred in only 28 patients (14.4%). AEs that occurred in 16 patients led to discontinuation from the study. The most frequently observed AEs were pain (8.2%), diarrhoea (7.7%), headache (6.7%), constipation (6.2%), nausea (6.2%) and hyperhidrosis (5.6%) (Table 6). Of the 15 patients experiencing diarrhoea, 12 had received OxyPR and three OXN PR during the previous double-blind phase. Seven patients experienced this AE within the first week of the extension phase. In nine patients, the diarrhoea was considered related to the study medication, suggesting the onset of action of naloxone; seven of these had received OxyPR and two OXN PR in the double-blind phase. There were four deaths, all of which were caused by cancer progression.

Table 5 Summary of adverse events (AEs) in the total exposure safety population and cancer patient subgroup.

	Total (n = 195)	Cancer patients (n = 35)
AEs, n	452	114
Patients with ≥1 AE	128 (65.6)	26 (74.3)
Treatment-related AEs, n	162	19
Patients with ≥1 treatment-related[a] AE	57 (29.2)	6 (17.1)
Severe AEs, n	39	20
Patients with ≥1 severe AE	28 (14.4)	12 (34.3)
Patients with ≥1 treatment-related[a] severe AE	9 (4.6)	2 (5.7)
SAEs, n	36	11
Patients with ≥1 SAE	21 (10.8)	10 (28.6)
Patients with ≥1 treatment-related[a] SAE	6 (3.1)	0
Patients who died	4 (2.1)	4 (11.4)

SAE, serious adverse event.

[a]Investigator considered the AE to be 'unlikely', 'possibly', 'probably' or 'definitely' related to study medication. Data are n (%) unless stated otherwise.

Table 6 Adverse events (AEs) occurring with an incidence of ≥5% in the total exposure safety population and the cancer patient subgroup.

	All patients (n = 195)	Cancer patients (n = 35)
Patients with ≥1 AE	128 (65.6)	26 (74.3)
Anaemia	3 (1.5)	2 (5.7)
Blood sodium decreased	3 (1.5)	2 (5.7)
Constipation	12 (6.2)	0
Decreased appetite	5 (2.6)	3 (8.6)
Diarrhoea	15 (7.7)	3 (8.6)
Dizziness	4 (2.1)	2 (5.7)
Dyspepsia	3 (1.5)	2 (5.7)
Haemoglobin decreased	2 (1.0)	2 (5.7)
Headache	13 (6.7)	3 (8.6)
Hyperhidrosis	11 (5.6)	1 (2.9)
Hypertriglyceridaemia	3 (1.5)	2 (5.7)
Influenza	8 (4.1)	2 (5.7)
Influenza-type illness	3 (1.5)	2 (5.7)
Metastases to CNS	2 (1.0)	2 (5.7)
Nausea	12 (6.2)	1 (2.9)
Neoplasm malignant	2 (1.0)	2 (5.7)
Pain	16 (8.2)	2 (5.7)
Somnolence	7 (3.6)	3 (8.6)
Vomiting	6 (3.1)	2 (5.7)

Data are n (%) unless stated otherwise. Adverse events (AEs) occurring with an incidence of ≥5% in the total exposure safety population or the cancer patient subgroup. Where the incidence was less than 5% in either the total group or the cancer subgroup, the incidence is shown for comparative purposes.

Of the 128 patients who experienced AEs, 57 patients (29.2%) had AEs that were considered by investigators to be related to study medication. The majority of related AEs had a low likelihood of causality and only three patients had definitely related AEs. There were 13 treatment-related SAEs in six patients (3.1%). Four (cholelithiasis, myocardial ischaemia, pleurisy, pneumonia) in two patients were only assessed as unlikely to be related to study medication. Five (drug ineffective, feeling cold, restlessness, hyperhidrosis, pulmonary embolism) in two patients were assessed as possibly related to study medication. Four SAEs (sinus bradycardia, dental caries, tooth loss, tooth disorder) in two patients were assessed as probably related.

3.4.2 Opioid withdrawal

The COWS and modified SOWS scores remained low a week after the switch from double-blind study medication to open-label OXN PR (Table 7). The mean SOWS scores in the week after the switch from double-blind medication were low and differed only slightly between patients who had continued on OXN PR (mean 4.95, median 3.0) and patients

Table 7 Clinic Opiate Withdrawal Scale (COWS) and modified Subjective Opiate Withdrawal Scale (SOWS) scores at Week 1 in the total exposure safety population.

	Double-blind phase medication		
	OXN PR (n = 100)	OxyPR (n = 95)	Extension phase (n = 195)
Modified COWS	1.09 (1.44); 1.0 [0–7] (n = 99)	1.61 (2.26); 1.0 [0–15] (n = 92)	1.34 (1.89); 1.0 [0–15] (n = 191)
Modified SOWS	4.95 (5.97); 3.0 [0–33] (n = 99)	5.72 (6.50); 4.0 [0–32] (n = 92)	5.32 (6.22); 3.0 [0–33] (n = 191)

Data are mean (SD); median [range].

who were switched from OxyPR (mean 5.72, median 4.0). The maximum recorded SOWS in both groups combined was >26 with a maximum of 33 in patients who had received OXN PR and 32 in patients who had received OxyPR previously. Three patients had SOWS scores >26, one of these patients discontinued the study, due to patient's choice.

Similarly, the COWS scores were low. The maximum COWS score was 15 and patients who had previously received OxyPR had minimally increased COWS scores at 1.61, while patients who remained on OXN PR had a mean of 1.09. These data are in line with the low number of AEs that were reported as 'drug withdrawal syndrome'. For both assessments, scores differed only slightly between patients according to their treatment during the double-blind phase. Two patients experienced drug withdrawal syndrome in the first week after the switch from OxyPR, and a third patient experienced drug withdrawal syndrome during the weeks 2–4. In weeks 5–24, no subject experienced an AE Drug withdrawal.

3.4.3 Other safety assessments

No clinically relevant changes were observed in physical examinations, vital signs and clinical laboratory test results. Abnormal vital sign values were infrequent and isolated and abnormal laboratory values were consistent with patients' underlying diseases. Clinically significant ECG findings which had not been present at baseline were occasional with no discernible relationship with treatment.

3.5 Cancer patient sub-analysis

Ongoing malignancies, including breast cancer, lung cancer and bone metastases, were recorded for 50 patients (20.6%) at screening, 35 of whom entered the extension study. The distribution of mean daily dose levels in cancer patients was generally similar to those of the total patient group (Table 2). The mean (SD) daily dose was 140 (28.7) mg and median (range) was 140 (100–180) mg.

Changes in the BFI during the study show that the largest decrease was seen in the first week (Fig. 2). The mean (SD) BFI in cancer patients decreased from 36.6 (26.26) to 29.0 (21.72) at Week 1 and 23.1 (22.60) at the end of the study. Average pain over the last 24 h remained stable and low over the 24 weeks in both groups, that is, in patients who received OxyPR in the double-blind phase as well as those who remained on OXN PR (Fig. 4). Similarly, the EQ-5D-3L index and EQ Health today score changed little during the study (Table 4).

The frequency of AEs, severe AEs, and SAEs were higher among cancer patients than in the total patient group, whereas the corresponding frequency of treatment-related AEs and SAEs was lower (Table 5). Common AEs in this subgroup were consistent with those in the total patient group (Table 6). Notably, no cancer patient-reported constipation as an AE.

4. Discussion

The prevalence of moderate or severe pain is high; European-wide surveys have reported that 56% of cancer patients and 19% of adults in the general population suffer from moderate-to-severe recurrent pain (Breivik et al., 2006; Breivik et al., 2009). Effective relief of moderate-to-severe chronic pain is often achieved by opioid analgesics such as OXN PR used according to management guidelines. For OXN PR, the dose should be titrated up to a maximum daily dose of 160/80 mg, as approved, to achieve effective analgesia and acceptable tolerability. For patients requiring higher doses of OXN, administration of supplemental prolonged-release oxycodone hydrochloride at the same time intervals should be considered, taking into account the maximum daily dose of 400 mg prolonged-release oxycodone hydrochloride. Controlled clinical studies in patients with cancer- and non-cancer pain have shown 120/60 mg daily to be effective and well-tolerated (Löwenstein et al., 2009; Ahmedzai et al., 2012). The randomized, double-blind, controlled phase of the current study showed efficacy and safety in doses up to 160/80 mg daily. This extension phase provides evidence that treatment with OXN PR in

daily doses up to 180/90 mg, is efficacious over a period of 24 weeks in typical population of chronic cancer and non-cancer patients suffering from severe pain of various origins (Simpson et al., 2008; Löwenstein et al., 2009; Ahmedzai et al., 2012).

In this study, bowel function, as measured by the BFI, improved in the first week of treatment and remained stable and low (mean BFI <34) thereafter. Comparison with the BFI reference range for non-constipated patients with chronic pain of 0–28.8 (Ueberall et al., 2011) shows that there was a clear overall trend towards normalization of the bowel function during extended OXN PR treatment. Patients who had received OxyPR during the previous double-blind study showed a clinically relevant improvement in BFI by the first week of OXN PR treatment in this extension study (Dupoiron et al., 2016). By the end of the study, the mean (SD) change in BFI from baseline in this patient group of −30.4 (26.15) was more than twice the threshold increment for clinical relevance, which is a decrease of 12 (Rentz et al., 2009). These results show that the onset of the naloxone effect in patients with OIBD occurs in the first week of treatment, and an improvement of bowel function is maintained under long-term treatment with OXN PR. In addition, the improvement in bowel function both in patients treated with OXN PR during the double-blind study phase as well as in patients who switched to OXN PR at the beginning of this extension study was maintained throughout treatment. In the group of patients with cancer, improvement in intestinal function (BFI) was lower than in the whole study group. This was probably due to the additional impact of cancer and deteriorating general condition of the patients.

Rescue medication in the form of laxatives was used in the first week of the extension phase by 2.6% of patients as needed and by 1.0% regularly. After the first week, when laxatives had to be prescribed as per treatment guidelines for patients on opioid therapy, only 13.3% took them regularly. Opioids were primarily taken as rescue medication on an 'as needed' basis and most patients did not receive a regular daily dose, or received the medication for a limited time period only.

SOWS and COWS scores, which are indicators of opiate withdrawal syndrome, did not give rise to concern, and remained low after the switch from the double-blind medication, indicating that the beneficial effects of naloxone up to 90 mg per day (as a component of OXN PR) on bowel function had not been offset by an increase in drug withdrawal effects. Similar results were observed in a study reported by Blagden et al. (2014).

Average pain over the last 24 h remained stable and low over the 24-week study, and showed the same pattern in different subgroups. While the EQ-5D-3L identified a small increase in patients unable to perform their daily tasks, the affected patients had already reported some problems with performing their usual activities at earlier visits. In addition, the chronic or progressive nature of underlying conditions (e.g. back pain or cancer) of the study population are likely to have contributed to a slight increase in this score. Overall QoL, which had improved during the double-blind phase (Dupoiron et al., 2017), and patient-reported health status similarly remained stable during the study.

Common AEs were consistent with the known effects of OXN PR. In addition, despite the use of higher oxycodone/naloxone doses than were used in previous studies of OXN PR, the frequency of treatment-related AEs (29.2% overall and 17.1% in the cancer patient subgroup) compares favourably with reported AE rates during long-term OXN PR treatment of patients with non-cancer pain (46.0%) (Blagden et al., 2014) and cancer pain (28.1%) (Ahmedzai et al., 2015). SAEs in only six patients were considered to be treatment related. Most SAEs were characteristic of the progression of underlying diseases in elderly patients with severe pain and other typical age-associated health problems, including cancer in 20% of patients. In this context, a rate of SAEs of approximately 10% over a period of 6 months was not considered to be unusually high.

In summary, this study demonstrated that OXN PR in daily doses of up to 180/90 mg over 24 weeks provides effective analgesia, improved bowel function and stable QoL in patients with OIBD and chronic cancer and non-cancer pain requiring around-the-clock opioid therapy.

Acknowledgements

Medical writing support provided by MedSciMedia Ltd.

Author contributions

B. Bosse: Data analysis, critical revision of the manuscript review and final approval of the version to be published. 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. Dupoiron: Investigator in this study, interpretation of the data, critical revision of the manuscript review and final approval of the

version to be published. M. Hopp: Study design, interpretation of the data, critical revision of the manuscript review and final approval of the version to be published. W. Kremers: Study design, 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 the manuscript review and final approval of the version to be published. A. Stachowiak: Investigator in this study, interpretation of the data, critical revision of the manuscript review and final approval of the version to be published.

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