Fixed ratio (2:1) prolonged-release oxycodone/ naloxone combination improves bowel function in patients with moderate-to-severe pain and opioid induced constipation refractory to at least two classes of laxatives

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ABSTRACT

Objective

The effects of combined oxycodone/naloxone prolonged release tablets (OXN PR) were investigated in patients with moderate-to-severe chronic cancer-related or non-cancer pain. All patients had opioid induced constipation (OIC) which persisted despite substantial laxative therapy.

Research design and methods

This pooled analysis included 75 patients with OIC at study entry that was refractory to at least two laxatives with different modes of action. Patients completed randomized, double-blind treatment with OXN PR 20–120 mg/day for either 12 weeks (OXN 9001: non-cancer pain study) or 4 weeks (OXN 2001: cancer-related pain study). Analgesia and bowel function were assessed using the Brief Pain Inventory Short Form and Bowel Function Index (BFI), respectively. Use of laxative medication and safety were assessed throughout the studies.

Clinical trial registration

NCT00513656, EudraCT 2005-002398-57, EudraCT 2005-003510-15.

Results

Statistically and clinically significant improvements in bowel function were observed following double-blind treatment with OXN PR. Mean (SD) reduction in BFI score was 21.2 (28.8) and comparable in patients with cancer-related (19.0 [28.9]) and non-cancer pain (23.3.[29.0]; P_0.0002). Furthermore, the proportion of patients with a BFI score within normal range (_28.8) increased from 9.5% at screening to 43.1% at Day 15 of OXN PR. While all patients used _2 laxatives of different classes at screening, during study treatment 36% stopped using laxatives (P50.001). OXN PR provided effective analgesia, evidenced by stable pain scores during study treatment, and there were no unanticipated adverse events.

Conclusions

OXN PR significantly improved bowel function and reduced the use of laxatives in patients with OIC, previously unresponsive to at least two different classes of laxatives. OXN also provided effective analgesia for patients with moderate-to-severe cancer-related pain and non-cancer-related pain.

INTRODUCTION

Chronic pain places a significant burden on patients, affecting many activities of daily living as well as resulting in loss of independence, anxiety and depression[1,2]. Moderate-to-severe chronic pain has a prevalence of approximately 20% in Europe, and is even more common in patients with cancer, affecting most individuals with advanced disease [1,3,4].

Opioid analgesics are effective treatments for moderate to severe cancer-related and non-cancer pain and are recommended in this setting[5–8]. However, as a therapeutic class, opioids are associated with side effects, including opioid-induced bowel dysfunction (OIBD). OIBD arises from the interaction of exogenous opioids with enteric μ-opioid receptors located throughout the gastrointestinal tract. This can result in inhibited gastric emptying, decreased peristalsis, decreased secretion of intestinal fluids, increased absorption of water as well as dysfunction of esophageal and anal sphincters. These effects can result in gastro-esophageal reflux, nausea and vomiting, and symptoms of opioid-induced constipation (OIC) including abdominal pain and distension, hard stools which are difficult to pass, hemorrhoids and incomplete evacuation[9–12]. OIC affects up to 80% of patients treated with opioid analgesia and is frequently reported to be the most bothersome side effect associated with this therapy[13–15]. OIC has a negative impact on patients' quality of life, and has also been shown to be associated with lower work productivity, absenteeism and significant utilization of healthcare resources[13,15–17].

Treatment guidelines recommend that laxatives should be used in conjunction with opioid analgesics in patients with cancer-related and non-cancer pain[7,8,18]. However, evidence is lacking regarding the type, dosage and timing of laxative therapy[19,20]. Many patients report that laxatives fail to relieve symptoms of OIC. For example, a large-scale study of patients taking opioid analgesia revealed that over half reported fewer than three bowel movements per week despite taking laxatives[13]. In this study, 44% of patients reported using two or more different types of laxatives in the preceding 3 months, and a similar proportion reported using laxatives on at least 5 days of the week[13]. Furthermore, despite taking laxatives, one-third of patients reduce the dosage or stop taking opioids in order to make it easier to have a bowel movement, thereby sacrificing effective pain relief[13].

Given the nature of chronic pain, effective management often requires prolonged opioid therapy. However, as well as the financial cost, bloating, flatulence and abdominal cramps associated with laxative treatments, it is noteworthy that continuous, long-term use of laxatives may lead to electrolyte imbalances as well as having a negative impact on daily activities due to loss of bowel control and unpredictable timing of laxation[17,21–24].

The opioid analgesic oxycodone (Oxy) has proven efficacy for the management of moderate-to-severe cancer related and non-cancer-related pain[25,26]. In order to address the opioid class-effect symptoms of OIC, Oxy was combined with the opioid-receptor

antagonist, naloxone in a prolonged-release formulation (OXN PR). Following oral administration, naloxone has ≤2% systemic availability due to extensive first-pass hepatic metabolism, and consequently acts on opioid receptors in the gastrointestinal tract where it has greater affinity than Oxy[27]. Importantly, the addition of naloxone to oxycodone was shown to be capable of counterbalancing oxycodone-induced delay of colonic transit, as measured with 99mTc-labelled tablets[28].

Clinical trials have demonstrated that OXN PR is associated with analgesia comparable with Oxy PR while providing significantly superior bowel function in patients with non-cancer-related pain and in those with cancer related pain[29–32]. These beneficial effects of OXN PR were associated with improvements in quality of life compared with previous analgesic therapy[33], and were prolonged, being observed during long-term treatment for up to 52 weeks[34,35]. Furthermore, the efficacy and safety of OXN PR in real-world treatment settings has been demonstrated in non-interventional studies involving over 10,500 patients with cancer-related pain and non-cancer related pain[36,37].

However, little is known about the effect of OXN in patients who have OIC which is particularly difficult to treat. This includes patients experiencing no relief from OIC despite taking several different types of laxatives. Therefore a pooled analysis of randomized, controlled trials was conducted, focused on patients with moderate to severe pain who were randomized to OXN PR and had OIC at screening, despite the use of two or more laxatives with different modes of action.

PATIENTS AND METHODS

Patients and study design

This pooled analysis comprised patients aged ≥18 years with moderate-to-severe, chronic pain that required round-the-clock opioid therapy, and had received OXN PR in prior double-blind, multicenter, randomized studies, designed to assess the efficacy and safety of OXN PR. At study entry, all patients included in this pooled analysis had OIC. Their OIC was associated with prior, non-study opioid therapy and persisted despite the use of at least two laxatives with different mechanisms of action (Anatomical Therapeutic Chemical [ATC] 4). The design of these studies has been described previously. In brief, Study OXN9001 was a pooled analysis of two Phase III studies of similar design (OXN3001; EudraCT: 2005-002398-57; and OXN3006; EudraCT: 2005-003510-15). Patients with non-cancer pain were randomized to 12 weeks of OXN PR or Oxy PR at doses equivalent to 20–50 mg/day (OXN3001)[32], or 60–120 mg/day of Oxy (OXN3006)[30], following a run-in period (7–28 days), in which patients were titrated to an effective analgesic dose of Oxy PR[30–32]. Study OXN2001 was a Phase II study of patients with moderate-to-severe cancer-related pain (ClinicalTrials. gov: NCT00513656). Following

a screening period (3–10 days), patients were switched from their pre-study opioid to treatment with OXN PR or Oxy PR for 4 weeks at doses of 20–120 mg/day (a run-in, dose-titration period was not included)[29].

In all studies, oral bisacodyl (10 mg/day) was permitted as rescue laxative medication (OXN9001: 72 hours after a bowel movement but could be taken sooner if patients exhibited discomfort; OXN2001: maximum of five doses in seven consecutive days). The studies were conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization Guidelines for Good Clinical Practice, were approved by local ethics committees, and all patients gave informed, written consent prior to enrolment.

Outcomes and assessments

The primary objective of this pooled analysis was to evaluate bowel function in patients randomized to OXN PR who had OIC at study entry, despite the use of two different classes of laxatives. This was performed using the validated Bowel Function Index (BFI; Copyright for the Bowel Function Index is owned by Mundipharma GmbH, Switzerland, 2002; the BFI is subject of European Patent Application Publication No. EP 1,860,988 and corresponding patents and applications in other countries)[38,39]. BFI score comprised the arithmetic mean score of three items rated on a numerical analogue scale (NAS) of 0–100: ease of defecation (0=easy/no difficulty to 100=severe difficulty), feeling of incomplete bowel evacuation (0=not at all to 100=very strong), and personal judgment of constipation (0=not at all to 100=very strong). BFI score was assessed at screening, start of double-blind treatment and end of double-blind treatment. Laxative use (bisacodyl and non-study laxatives) throughout the studies was

documented. Analgesic efficacy was monitored using the Brief Pain Inventory Short Form (BPI-SF) to assess average pain over the last 24 hours (single question on NAS; 0=no pain to 10=worse pain ever). Use of oxycodone immediate release tablets (Oxy IR) as analgesic rescue medication throughout the studies was recorded. Safety was monitored via the documentation of adverse events (AEs, classified by system organ class and Medical Dictionary for Regulatory Activities [MedDRA] preferred terms) and serious adverse events (SAEs); monitoring of vital signs, hematology, blood chemistry, and electrocardiograms.

Statistical methods

Analyses were performed in the intention-to-treat population. The change in BFI score from the start to end of study treatment was analyzed using paired t-tests, with a change of ≥12 points being considered clinically meaningful[38]. Change in BPI-SF score and frequency of analgesic rescue medication use (Oxy IR) during study treatment were assessed using signed-rank tests, while change in laxative use was assessed using a

McNemar test. All statistical analyses were performed using SAS version 9.1.3 software (SAS Institute Inc., Cary, NC, USA).

RESULTS

Patient characteristics and study treatment

In total 75 patients with chronic, moderate-to-severe pain and OIC at study entry despite the use of at least two laxatives with differing mechanisms of action had been randomized to double-blind treatment with OXN PR. Just over half the patients (n=40, 53.3%) had cancer related pain (OXN2001) and 46.7% (n=35) had non-cancer pain (OXN9001). There were no significant differences in the demographic characteristics of the two groups. Median (range) age was 62.0 (40, 80) years (OXN2001:61.5 [40, 80]; OXN9001: 62.0 [40, 77]) and approximately two-thirds of patients (69.3%) were ≤65 years (OXN2001: 65.0%; OXN9001: 74.3%). There was a trend for more women with non-cancer pain (71.4%) versus cancer pain (47.5%). OXN PR dosage remained relatively stable throughout the trials. Across the studies, the mean daily dose of OXN PR at the start of treatment (28.5 mg/day) increased by 6.0 mg/day at the end of the double-blind treatment. Mean changes in OXN PR dosage during treatment were similar in patients with cancer-related pain and non-cancer pain (OXN2001: 7.0 mg/day, OXN9001: 4.9 mg/day).

Bowel function index

Overall, the mean (SD) BFI score at screening was 62.5 (18.7) and was comparable in patients with cancer-related pain and non-cancer pain (OXN2001: 62.8 [17.4], OXN9001: 62.1 [20.4]). At the start of the double-blind treatment phase, high BFI scores were recorded (OXN2001: 66.4 [15.9], OXN9001: 61.3 [23.2]). Improvements in bowel function, indicated by a decrease in BFI score, were observed at the end of the double-blind treatment with OXN PR. Overall, BFI score decreased by a mean (SD) of 21.2 (28.8) to 43.0 (31.1). Patients with cancer-related pain had a decrease of 19.0 (28.9) after a mean of 24.7 days of treatment, while patients with non-cancer related pain experienced a decrease in BFI score of 23.3 (29.0) following 69.5 days of treatment. The reductions in BFI score were clinically and statistically significant in both groups of patients (P≤0.0002; Figure 1).

The shorter mean duration of treatment with OXN PR in patients with cancer-related pain compared with non-cancer related pain reflected differences in the treatment durations defined in the study protocols (4 weeks versus 12 weeks). In addition to the significant improvements in BFI scores associated with OXN PR, an increase in the proportion of patients who had a BFI score within the normal range (validated as≤28.8 in non-constipated patients with chronic pain[39]) was observed within the first 2 weeks of treatment.

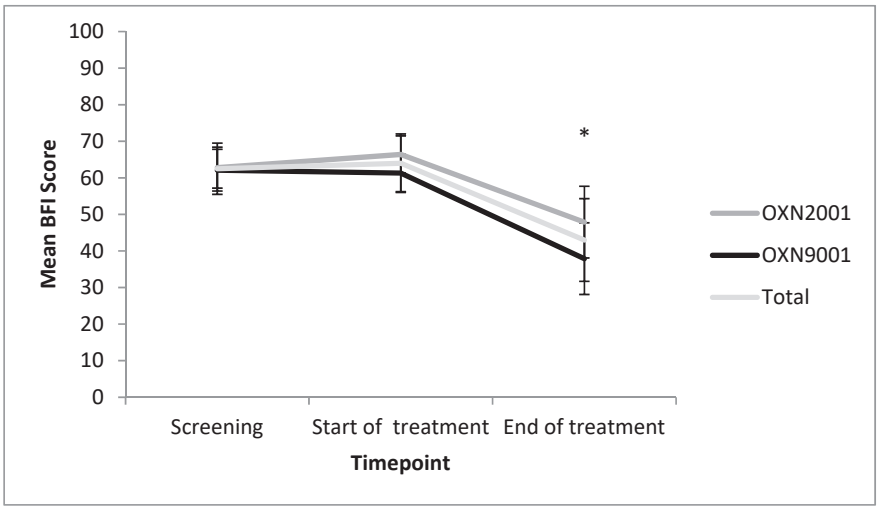

Figure 1. Bowel Function Index during treatment.
Mean ± confidence interval. BFI score 0–28.8 is the reference range for non-constipated patients with chronic pain[39].
*BFI score at end of double-blind treatment minus score at start of double-blind treatment, assessed using paired t-test: OXN2001 P=0.0002; OXN9001<.0001; and Total P<0.0001. OXN2001: patients with cancer-related pain randomized to OXN PR for 4 weeks. OXN9001: patients with non-cancer-related pain randomized to OXN PR for 12 weeks.

Prior to randomization, 9.5% of patients had a BFI score ≤28.8 (5.1% in OXN2001 and 14.3% in OXN9001). At Day 8 of OXN PR, this increased to 31.9% (27.8% in OXN2001 and 36.4% in OXN9001), and at Day 15 of OXN PR, 43.1% (36.4% OXN2001 and 50.0% OXN9001) had a normal BFI score (Table 1).

Table 1: Patients with normal Bowel Function Index score.

		Duration of treatment with OXN PR					
BFI score ≤28.8	Screening % (n/N)	Day 1 % (n/N)	Day 8 % (n/N)	Day 15 % (n/N)	Day 29 % (n/N)	Day 57 % (n/N)	Day 85 % (n/N)
OXN2001	5.1 (2/39)	0 (0/40)	27.8 (10/36)	36.4 (12/33)	22.2 (8/36)	–	–
OXN9001	14.3 (5/35)	8.6 (3/35)	36.4 (12/33)	50.0 (16/32)	44.8 (13/29)	48.1 (13/27)	40.0 (14/35)
Total	9.5 (7/74)	4.0 (3/75)	31.9 (22/69)	43.1 (28/65)	32.3 (21/65)	–	–

BFI score 0–28.8 is the reference range for non-constipated patients with chronic pain.
OXN2001: 40 patients with cancer-related pain randomized to OXN PR for 4 weeks
OXN9001: 35 patients with non-cancer-related pain randomized to OXN PR for 12 weeks

Laxative use

All patients in this analysis had been using at least two laxatives of different mechanistic classes at study entry without success. Contact laxatives (n=72, 96.0%) and osmotically

acting laxatives (n=67, 89.3%) were most commonly used, while enemas, stool softeners/emollients and other laxatives were used by 8 (10.7%), 4 (5.3%) and 12 (16.0%) patients, respectively. In total, 64.0% (n=48) required the study laxative (bisacodyl) during study treatment. Four patients (5.3%) used non-study laxatives in addition to bisacodyl: one patient in OXN9001 (polyethylene glycol and lactulose) and three patients in OXN2001 (lactulose [n=2], polyethylene glycol [n=1]). During study treatment, no patients started using laxatives while 36.0% stopped using laxatives (McNemar test, P<0.001). As expected, use of the study laxative was more frequent in patients with cancer-related pain (82.5%; median [range] 6.0 [1–20] tablets) than in those with non-cancer-related pain (42.9%; 10 [1–36] tablets). Mean daily doses of study laxative were 2.1 mg for patients in OXN2001 and 4.3 mg for those in OXN9001. Data indicate that study laxative was used as needed; for patients with non-cancer pain, the mean number of days with study laxative use (4.2 days) was less than the mean number of days receiving study medication (69 days) (Table 2).

Table 2: Use of study laxative (bisacodyl) during double-blind treatment with OXN PR.

BFI Score		**OXN2001 (n=40)**	**OXN9001 (n=35)**
Any study laxative used	% (n/N)	82.5 (33/40)	42.9 (15/35)
Any non-study laxative used	% (n/N)	NR	2.9 (1/35)
Number of days study laxative used	n	NR	15
	Mean (SD)	NR	4.2 (2.8)
	Median	NR	5.0
	Min, max	NR	1, 8
Duration of study treatment (days)	n	33	15
	Mean (SD)	24 (7.5)	69 (33)
	Median	28	77
	Min, max	1, 34	7, 146
Daily dose of bisacodyl (mg/day)	n	33	15
	Mean (SD)	2.1 (1.7)	4.3 (4.0)
	Median	1.82	3.1
	Min, max	0.2, 8.3	0.3, 11.3

OXN2001: 40 patients with cancer-related pain randomized to OXN PR for 4 weeks
OXN9001: 35 patients with non-cancer-related pain randomized to OXN PR for 12 weeks

This is in contrast to the period prior to receiving double-blind treatment with OXN PR in which all patients used at least two laxatives of different ATC class. At this time, 67% of patients used at least one laxative on a daily basis (70% of patients with cancer-related pain and 63% of patients with non-cancer pain).

Analgesic efficacy and safety

Overall, there was no significant difference in 'average pain over the last 24 hours' scores from the start to end of double-blind treatment with OXN PR. While pain response remained stable in patients with non-cancer related pain (OXN9001: mean change in score 0.1, P=0.481), there was a non-significant trend for improvement in pain scores reported by patients with cancer related pain (OXN2001: mean change in score -0.4, P=0.311). Use of Oxy IR analgesic rescue medication decreased following double-blind treatment with OXN PR. In patients with cancer-related pain (OXN2001) there was a significant decrease in the median dose of rescue medication (Oxy IR) from the start of study treatment (Days 1–7: 3.93 mg) to the end of study treatment (Days 29–35: 1.25 mg; P¼0.0018). Similarly, in patients with non-cancer related pain median dose of rescue medication (Oxy IR) in the run-in period (5.0 mg) was significantly greater than that at the end of study treatment (Days 57–84; 0.3 mg; P=0.006). The percentage of patients who used Oxy IR remained stable throughout double blind treatment with OXN PR in both studies.

AEs related (definitely, probably or possibly) to study medication were reported in one-third of patients

(OXN2001: 27.5%, OXN9001: 40.0%). SAEs were more common in patients with cancer-related pain (OXN2001: 25.0%, OXN9001: 2.9%). All four deaths during the study occurred in patients with cancer-related pain but none were considered related to study medication. During double-blind treatment with OXN PR, the most common AEs were nausea (9.3%), constipation (9.3%) and vomiting (8.0%; Table 3).

Table 3: All causality adverse events occurring during double-blind treatment with OXN PR (≥2 patients).

System organ class and MedDRA preferred term	Total (N=75) n (%)
Blood and lymphatic system disorders	**2 (2.7)**
Anaemia	2 (2.7)
Lymphopenia	2 (2.7)
Gastrointestinal disorders	**27 (36.0)**
Abdominal pain	2 (2.7)
Abdominal pain upper	4 (5.3)
Constipation	7 (9.3)
Diarrhoea	2 (2.7)
Dry mouth	2 (2.7)
Nausea	7 (9.3)
Vomiting	6 (8.0)
General disorders and administrative site conditions	**21 (28.0)**
Asthenia	5 (5.3)
Drug withdrawal syndrome	2 (2.7)
Fatigue	3 (4.0)

Table 3: All causality adverse events occurring during double-blind treatment with OXN PR (≥2 patients). (*continued*)

System organ class and MedDRA preferred term	Total (N=75) n (%)
Odema peripheral	4 (5.3)
Pain	4 (5.3)
Pyrexia	2 (2.7)
Investigations	**16 (21.3)**
Blood glucose increased	2 (2.7)
Haemoglobin decreased	3 (4.0)
Neutrophil count increased	2 (2.7)
Metabolism and nutritional disorders	**9 (12.0)**
Anorexia	3 (4.0)
Hyperkalaemia	3 (4.0)
Hyperuricaemia	2 (2.7)
Hypoalbuminaemia	3 (4.0)
Hypocalcaemia	2 (2.7)
Neoplasms (benign, malignant, unspecified)	**9 (12.0)**
Cancer pain	4 (5.3)
Malignant neoplasm progression	4 (5.3)
Nervous system disorders	**12 (16.0)**
Dizziness	2 (2.7)
Headache	4 (5.3)
Respiratory, thoracic and mediastinal disorders	**6 (8.0)**
Dyspnoea	3 (4.0)
Skin and subcutaneous disorders	**6 (8.0)**
Hyperhidrosis	3 (4.0)
Pruritis	2 (2.7)

Adverse events reported documented in only one patient are not shown
OXN2001: 40 patients with cancer-related pain randomized to OXN PR for 4 weeks
OXN9001: 35 patients with non-cancer-related pain randomized to OXN PR for 12 weeks

DISCUSSION

This pooled analysis of randomized clinical trials demonstrates that OXN PR is associated with significantly improved bowel function in patients with moderate-to-severe pain and OIC that is refractory to at least two different ATC class 4 laxatives. Switching from opioid analgesic plus multiple laxatives to OXN PR was associated with statistically significant and clinically relevant improvements in BFI scores as well as significant reductions in the use of laxatives.

Apart from the underlying cause of pain, there were no notable differences between patients with cancer-related pain and non-cancer-related pain in terms of demographic factors and dose of OXN PR received during the studies. At screening, when patients were receiving opioid analgesia of any type and at least two different types of laxatives, high BFI scores were observed in both groups (mean score 62.5), indicating these patients were suffering with constipation. While BFI scores at the start of treatment were greater in patients with cancer-related pain (66.4), statistically significant and clinically relevant improvements in OIC were observed in both groups of patients at the end of double-blind treatment with OXN PR (mean reductions in BFI scores of 19.0 and 23.3 points, respectively, P≤0.002). It is noteworthy that individuals with cancer-related pain received OXN PR for a shorter duration than those with non-cancer-related pain (4 weeks versus 12 weeks), since the design of the OXN2001 trial reflected the limited life expectancy of these patients. The positive effect of OXN PR on bowel function is further emphasized by the finding that the proportion of patients who had a BFI score within the normal range (≤28.8) increased by over four-fold from screening (9.5%) to Day 15 of OXN PR (43.1%).

In addition to the significant improvements in bowel function, OXN PR was also associated with reduced use of laxatives. While all patients were using at least two different classes of laxatives at screening, not all patients required laxatives during study treatment; 36.0% of patients stopped using laxatives and no patients started using laxatives during double-blind treatment with OXN PR (P<0.001). Furthermore, for patients with nonmalignant pain (OXN9001), the mean number of days with study laxative use (4.2 days) was approximately two-thirds less than the mean number of days receiving study medication (15.4 days). More patients with cancer-related pain (82.5%) used study laxative during study treatment compared with those with pain of a non-cancer origin (42.9%). This difference may be due to the other etiologies of constipation in patients with cancer in addition to opioid medication, including the malignancy itself, general debility, less mobility, other medications such as chemotherapeutic agents and concomitant diseases[40,41].

While treatment guidelines recommend laxatives are prescribed to be used in conjunction with opioid analgesics in patients with cancer-related and non-cancer pain, many patients report that laxatives fail to relieve symptoms of OIC and/or are associated with unpleasant complications[7,8,13,15,18,22,23]. Given the unique etiology of OIC and the effects of opioids on neural activity, motility and secretion throughout the entire gastrointestinal tract[11], it is unsurprising that laxatives frequently fail to counteract the symptoms of OIC[13,15]. Instead, treatment of OIC should target the etiology of this condition via a μ-opioid receptor mediated approach such as that of naloxone (a non-selective opioid antagonist), rather than just focus on symptomatic management[10,11].

As demonstrated in previous studies, OXN PR can significantly improve bowel function without affecting the pain relief observed with Oxy PR in patients with moderate-to-severe chronic pain[29–32]. This pooled analysis demonstrates that these effects are also valid for patients with persisting OIC despite the use of at least two different types of laxatives, and provides further confirmation that naloxone addresses OIC from a pathophysiological point of view rather than merely a symptomatic standpoint. In this pooled analysis, OXN PR provided effective analgesia for patients with moderate-to-severe pain with OIC that is refractory to at least two different classes of laxatives. The stable average pain scores during study treatment were comparable to observations in the patients randomized to Oxy PR in the primary studies for OXN2001 and OXN9001[29,31]. These findings add to the substantial body of evidence that addition of naloxone to Oxy PR (in the combination of OXN PR) can prevent symptoms of OIC while not interfering with the pain relief obtained with Oxy PR[42,43].

CONCLUSION

In summary, the results of this pooled analysis add to the body of evidence for the unique mechanism of action and therapeutic value of OXN PR. In patients with persisting OIC despite the use of two different classes of laxatives, OXN PR resulted in a significant and clinically relevant improved bowel function, significantly reduced the use of laxatives, and provided effective analgesia for patients with moderate-to-severe cancer-related pain and non-cancer related pain.

TRANSPARENCY

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