

# **Prolonged release oxycodone and naloxone treatment counteracts opioid induced constipation for patients with severe pain compared to previous analgesic treatment.**

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## ABSTRACT

### Objective

Treatment with prolonged-release oxycodone/naloxone (PR OXN) has been shown to improve opioid induced constipation (OIC) in constipated patients. This publication reports on a real-life observational study investigating the efficacy of PR OXN with regard to bowel function in patients switching to PR OXN from WHO-step 1, step 2 and step 3 opioids.

### Methods

Patients with chronic pain experiencing insufficient pain relief and/or unacceptable side effects were switched to PR OXN and monitored in this observational study with respect to efficacy regarding bowel function and efficacy regarding pain relief in comparison with previous analgesic therapy. A patient was considered responder with respect to efficacy if this assessment was 'slightly better', 'better' or 'much better' compared with previous therapy. Bowel function index, pain intensity, quality of life, laxative medication use, and safety analgesic were also evaluated.

### Results

1,338 patients (mean (sd) age 64.3 (14.9), 63% female) were observed for 43 [3-166] days (median [range]) during treatment with PR OXN. Overall response rate regarding bowel function efficacy was 82.5%. Patients with symptoms of constipation at study entry obtained a clinically relevant improvement of the bowel function index (BFI) within the first 2 weeks of PR OXN treatment. Non-constipated patients at study entry maintained normal bowel function despite switching to treatment with the opioid PR OXN.

### Conclusion

In conclusion, treatment with PR OXN results in a significant and clinically relevant improvement of bowel function. During the observation of the treatment with PR OXN patients reported an improvement of QoL. More interestingly, non-constipated patients maintained a normal bowel function, showing prevention of constipation despite the use of an opioid.

## INTRODUCTION

The prevalence of chronic pain in adults is about 19% in Europe<sup>1</sup>. Chronic severe pain, has important implications for the individual's quality of life and is a major public health challenge because of the impact on work performance and the increased use of health-care services<sup>2</sup>.

Strong opioids are a treatment option for pharmacological management of chronic moderate to severe pain of malignant and non-malignant origin<sup>3-6</sup>. However, 30% of the patients with malignant pain and 12% with non-malignant pains treated with an opioid do not achieve an adequate level of analgesia and/or suffer from intolerable or dose-limiting adverse effects<sup>7</sup>. Opioid-induced constipation (OIC) is the most common and most dominant adverse effect of opioid treatment<sup>8</sup> affecting up to 80% of patients treated with opioids<sup>9-11</sup>. Opioids contribute to OIC by activation of opioid receptors in the gastrointestinal wall leading to reduced motility of the gut and opioids can increase circular muscle activity (hence causing cramping pain) at the expense of longitudinal muscle. In addition, opioids contribute to OIC by increasing water withdrawal from the bowel<sup>8-11</sup>. OIC negatively impacts the patient's quality of life<sup>12</sup>, resulting in a lack of compliance in up to one third of the patients<sup>10</sup> potentially leading to insufficient pain relief. Moreover, OIC can in itself also be a cause for pain; the majority of patients with OIC report pain caused by OIC. Pain caused by OIC may result in more discomfort than pain caused by the underlying condition<sup>10, 13, 14</sup>. In contrast to other opioid-related side effects OIC is unlikely to improve over time and most patients do not develop tolerance to OIC<sup>10, 15-17</sup>.

Treatment of OIC comprises general non-pharmacological measures, like dietary advices and exercise, and the treatment with non-specific laxatives like bisacodyl, poly ethylene glycol with electrolytes and lactulose. However, about half of all opioid treated patients requiring laxatives do not achieve satisfactory relief from OIC, as most used laxative treatments for OIC are non-specific and do not target the underlying cause of OIC<sup>17, 18</sup>. Furthermore, laxatives themselves may lead to gastrointestinal adverse events and complications<sup>17</sup>.

Prolonged release oxycodone/naloxone (PR OXN) is a fixed combination of oxycodone/naloxone. When co-administered orally with oxycodone, naloxone counteracts OIC by antagonizing opioid receptors in the gastrointestinal wall, while its limited availability following first pass metabolism ensures its lack of interference on the analgesic effect of oxycodone mediated by activation of opioid receptors in the central nervous system<sup>19</sup>. In several randomized controlled trials PR OXN has shown to provide effective pain relief, while effectively counteracting OIC<sup>20-27</sup>. Several prospective, observational studies confirmed the efficacy of PR OXN in real-life studies<sup>28-30</sup>.

In this real-life observational study, the efficacy of PR OXN regarding bowel function was evaluated in patients with severe pain switching from WHO-step 1, step 2 and/or step 3 medication to PR OXN due to insufficient pain relief and/or unacceptable side effects in daily clinical practice in Belgium, taking into account previous used medication and constipation status at study entry.

## METHODS

### Study design and patient population

This publication describes the results of a phase IV, open label, multicenter, prospective, observational, real-life study conducted in Belgium between April and December 2011 approved by the ethical committees of the participating centers.

The decision to switch to open-label PR OXN preceded the decision to participate in the study and written informed consent was obtained before study entry. Adult patients with severe pain previously treated with WHO-step 1, step 2 and/or step 3 (excluding PR OXN) analgesics that had been switched to PR OXN because of insufficient pain relief and/or unacceptable side effects on their previous medication were consecutively included and treatment with open-label PR OXN as in daily clinical practice was monitored. Unacceptable side effects were defined as side effects that could not be tolerated by the patient. Patients were excluded in case of alcohol abuse, a history of active drug abuse, use of hypnotics or CNS depressants that might pose a risk of additional CNS depression, opioid therapy for opioid addiction, confirmed diagnosis of irritable bowel syndrome, evidence of clinically significant GI disease, and abnormalities of the GI tract or suffering from diarrhea and/or opioid withdrawal.

At the first baseline visit, patients were switched from their previous analgesic medication to the most appropriate twice-daily PR OXN dose (5 mg/2.5 mg, 10 mg/5 mg, 20 mg/10 mg or 40 mg/20 mg) according to the physician's judgment, taking into account that PR OXN is as effective for pain relief as oxycodone. Pain intensity and bowel function were recorded at the first baseline visit (visit 1) and at two follow-up visits (visit 2 and 3) during PR OXN treatment as in daily clinical practice.

Due to the observational real-life study design follow-up of patients was performed as in daily practice. In daily practice follow-up of patients during treatment differs per physician, therefore no fixed time points were set for the follow-up visits (visit 2 and 3). For efficacy analyses over time (efficacy regarding pain relief and efficacy regarding bowel function) the following intervals were defined; a)  $2 \pm 2$  weeks (visits on day 1 -28 after first visit) b)  $6 \pm 2$  weeks (visits on day 29- 56 after first visit); c)  $11 \pm 3$  weeks (visits day 57-98) and d)  $17 \pm 3$  weeks (visits day 98-140). For patients with more than one visit in one

time period, only the last visit in that period was considered for analysis of the efficacy endpoints.

BFI was analyzed at baseline (visit 1) and follow-up visits (visit 2 and 3) as well as over time (baseline,  $2\pm 2$  weeks,  $6\pm 2$  weeks,  $11\pm 3$  weeks and  $17\pm 3$  weeks). Data on laxative use, and adverse drug reactions were recorded over the period between visit 1 and 2 at visit 2, and over the period between visit 2 and 3, at visit 3. Quality of life was evaluated at the first and last study visit per patient (see supplementary table 1 for an overview of the study and study schedule).

### Outcome measurements

Outcome measurements included efficacy of PR OXN regarding bowel function compared to the previous analgesic treatment as evaluated by the physician using a 7-point ordinal scale (much worse, worse, slightly worse, same, slightly better, better and much better) and bowel function was also evaluated with the (Bowel Function Index ([BFI]<sup>31,32</sup>; Copyright for the BFI is owned by Mundipharma Laboratories 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).

For analysis, the 7-point physician evaluation scale was converted to a binary scale, where patients were considered responder if their bowel function during PR OXN treatment was evaluated as 'slightly better', 'better', or 'much better'.

The BFI is the arithmetic mean value of the patients' evaluation on the difficulty of bowel movement, feeling of incomplete bowel evacuation and personal judgment of constipation during the last 7 days, each scored from 0 (no problem/no difficulty) to 100 (severe difficulty/problem). A BFI  $< 28,8$  is validated as a normal bowel function<sup>33</sup> and a change in BFI  $\geq 12$  is considered as a clinically relevant change in bowel function<sup>31</sup>.

Outcome measurements for pain relief included the efficacy of PR OXN regarding pain relief compared to the previous analgesic treatment as evaluated by the physician using a 7-point ordinal scale (much worse, worse, slightly worse, same, slightly better, better and much better). Pain relief was also evaluated with the Numeric Rating Scale ([NRS] from 0 to 10).

For analysis, the 7-point physician evaluation scale was converted to a binary scale, where patients were considered responder if their pain relief during PR OXN treatment was evaluated as 'slightly better', 'better', or 'much better'. The percentages of patients using laxatives or analgesic rescue medication at the follow-up visits were calculated. The quality of life of patients was evaluated via the standardized EuroQoL (EQ-5D) questionnaire with 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The total EQ-5D score was calculated using Belgian population based tariffs that could range between -0.158 (all criteria scored a value of 3) and 1

(perfectly healthy). Additionally, patients assessed their QoL using the EQ-5D VAS (from 0 to 100, worst to best possible health status), indicating the patient's self-rated health.

### **Ethical considerations**

The study was registered with the Federal Agency for Medicinal Products and Health Products in Belgium (study code OXN9510) and was registered on clinicaltrials.gov with the identifier NCT01983137. The study was conducted in accordance with all applicable ethical guidelines and legislations. All patients provided written informed consent before inclusion.

### **Statistics**

All data were analyzed by descriptive statistics and statistical comparisons for all study parameters over time and between previous analgesic WHO-step treatments groups were performed. Patients were categorized by the previous WHO step group based on the highest WHO step group. All efficacy endpoints were analyzed for the full analysis (FA) population, defined as all eligible patients who received at least one dose of PR OXN and had at least one post-dose evaluation; safety endpoints were analyzed for the safety population, defined as all patients who received at least one dose of PR OXN and for whom at least one post dose safety assessment was recorded. Additionally, post hoc analyses on all efficacy parameters were performed on patients with symptoms of constipation ( $BFI \geq 28.8$ , constipated patients) and without symptoms of constipation ( $BFI < 28.8$ , non-constipated patients) at study entry.

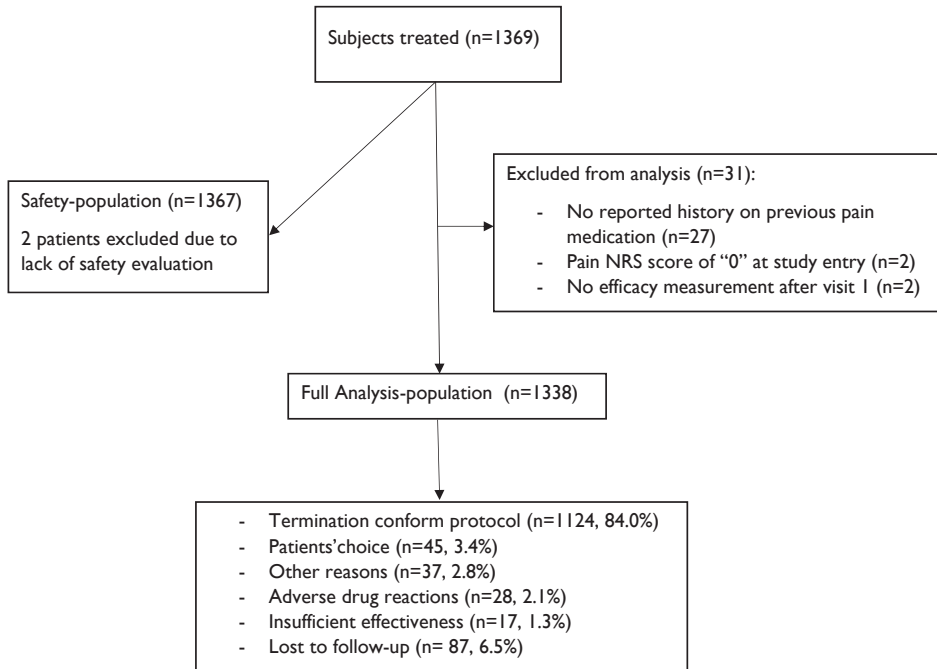
ANOVA and two-sample t-tests were used to compare subgroups at baseline and to compare changes from study entry and at last visit in bowel function (BFI), pain intensity (NRS) and QoL (EQ-5D) between the different subgroups. Categorical variables were compared using the Fisher's exact test.

## **RESULTS**

### **Patient population and demographic characteristics**

229 general practitioners and 55 specialists screened 1,429 patients experiencing severe pain (272 patients were screened by specialists and 1,157 by GPs), of whom 1,369 patients were treated with PR OXN. The safety population consisted of 1,367 patients of whom safety evaluations were available. 31 patients were excluded from the full analysis population (FA-population) because there were no data available on previous analgesic treatment ( $n=27$ ) or pain NRS score was "0" at study entry ( $n=2$ ) or follow up data were unavailable ( $n=2$ ), rendering 1,338 patients in the full analysis (FA)-population (Figure 1). The vast majority of patients (84.0%) terminated the study conforming to the protocol.

Reasons for early study discontinuation were adverse drug reactions (2.1%), insufficient effectiveness (1.3%), patients choice (3.4%), other reasons, such as planned surgical procedures and interventions (2.8%) and due to the observational nature of the study lost to follow-up (6.5%).



**Figure 1.** Flow diagram of the patients' disposition

Patient demographics and characteristics for the overall population and the analyzed subgroups are summarized in Table 1. The mean age of the overall population was  $64.3 \pm 14.9$  years, and 63% were female. Significantly more constipated patients (defined by a BFI > 28.8 at study entry) were older ( $p < 0.001$ ) and of female gender ( $p = 0.039$ ). The majority of patients suffered from non-malignant pain (77%), mainly caused by osteoarthritis (53%), low back pain (49%) and neuropathic pain (34%) (multiple pain indications could be chosen for one patient resulting in a sum > 100%). Nearly a quarter of the patients (23%) suffered from malignant pain, mainly caused by cancer of lung (16%), breast (16%), colon (16%) and prostate (10%). For patients with pain of malignant origin the majority suffered pain due to metastatic disease ( $n = 127$ ), 41 suffered from advancing disease and 20 suffered from post-treatment/post-operative pain. For 121 patients no specifications were given. Most malignant as well as non-malignant pain patients were treated by their GP (242 and 861 patients, respectively).

**Table 1.** Demographics and baseline characteristics of patients (Full Analysis-population)

	Previous WHO Step Analgesic			Bowel function		Total
	Step 1 n = 142	Step 2 n = 625	Step 3 n = 571	Non-constipated n=289	Constipated n=1,048	N = 1,338
<b>Age in years</b>						
Mean ± SD	63.0±15.6	63.8±14.9	65.0±14.7	60.8±15.2	65.2±14.7	64.3±14.9
<b>Gender: %Female</b>						
(n/N)	57.7% (82/142)	62.2% (389/625)	65.3% (373/571)	57.8% (167/289)	64.5% (676/1048)	63.1% (844/1338)
<b>Type of pain</b>						
Malignant % (n/N)	16.4% (23/140)	19.6% (122/621)	28.8% (164/570)	17.8% (51/287)	24.7% (258/1043)	23.2% (309/1331)
Non-malignant % (n/N)	83.6% (117/140)	80.4% (499/621)	71.2% (406/570)	82.2% (236/287)	75.3% (785/1043)	76.8% (1021/1331)
<b>Bowel Function Index (BFI)</b>						
Mean ± SD	31.8±26.4	47.7±27.6	65.3±23.0	10.4±9.3	65.4±17.8	53.5±27.9
<b>Pain intensity (NRS)</b>						
Mean ± sd	7.3±1.3	7.7±1.1	6.7±2.0	7.6±1.3	7.2±1.7	7.2±1.7
<b>Bowel function</b>						
BFI ≥28.8, % (n/N)	50.4% (71/141)	72.8% (455/625)	91.4% (522/571)	n.a	n.a.	78.4% (1048/1337)
<b>EQ-5D Total Score</b>						
Mean ± SD	0.32±0.26	0.25±0.23	0.26±0.26	0.27±0.24	0.26±0.25	0.26±0.25
<b>Reasons for switch</b>						
Insufficient effectiveness	94.5%	94.9%	50.1%	93.8%	73.9%	78.9%
Unacceptable side effects	17.9%	56.9%	86.2%	33.4%	67.7%	65.4%

At the start of PR OXN treatment, 10.6% of patients were previously treated with WHO step 1, 46.7% with WHO step 2 and 42.7% with WHO step 3 analgesics. Patients with malignant pain were more often treated with WHO-step 3 analgesics than with WHO-step 1 and WHO-step 2 analgesics ( $p < 0.001$ ). At study entry, the pain score was significantly lower in the WHO-step 3 group compared to the other WHO-step groups ( $p < 0.001$ ) and pain score of constipated patients was significantly (but not clinically relevant) lower compared to non-constipated patients ( $p = 0.002$ ).

Mean BFI at study entry was high ( $53.5 \pm 27.9$ ), with significant differences between the WHO-step groups ( $p < 0.001$ ). Interestingly, the percentage of constipated patients at study entry (BFI > 28.8) in the WHO-step 1 group was already 50.4% and this was even higher in the WHO-step 2 group and in the WHO-step 3 group (72.8% and 91.4% respectively). The overall mean EQ-5D total score at study entry was low  $0.26 \pm 0.25$ , with statistically significant differences between the WHO-step groups, with the lowest scores for the WHO step 2 and WHO step 3 group (0.25 and 0.26 respectively ( $p = 0.005$ )).



## PR OXN treatment

Overall, patients were followed in the study for mean  $\pm$  sd 47.8 $\pm$ 25.2 days (N=1338) and 45.5% were followed between 4 to 8 weeks with no significant differences between the subgroups. The mean daily dose of PR OXN increased from 11.6 mg at visit 1 to 15.2 mg at last visit in the total group (Table 2).

The highest dose was prescribed in WHO-step 3 pretreated patients and the mean dose of PR OXN was numerically higher for constipated patients at study entry. However, there were no statistically significant differences in mean PR OXN dose between the three WHO-step subgroups and the two bowel function subgroups.

**Table 2.** Daily dose of the oxycodone component of PR OXN

	Previous WHO step analgesic			Bowel function		Total
	Step 1	Step 2	Step 3	Non-constipated	Constipated	
<b>Daily Oxycodone Dose (mg) Visit 1</b>						
<i>Mean <math>\pm</math> SD</i>	7.5 $\pm$ 5.2	8.8 $\pm$ 7.2	15.8 $\pm$ 13.3	8.7 $\pm$ 6.9		12.5 $\pm$ 11.4
<i>(N)</i>	(141)	(622)	(565)	(287)		(1041)
<b>Daily Oxycodone Dose (mg) Visit 2</b>						
<i>Mean <math>\pm</math> SD</i>	8.4 $\pm$ 5.3	10.8 $\pm$ 8.1	18.4 $\pm$ 14.6	9.9 $\pm$ 7.5		14.8 $\pm$ 12.6
<i>(N)</i>	(140)	(622)	(557)	(284)		(1034)
<b>Daily Oxycodone Dose (mg) Visit 3</b>						
<i>Mean <math>\pm</math> SD</i>	8.6 $\pm$ 5.7	12.3 $\pm$ 10.4	20.0 $\pm$ 16.8	11.0 $\pm$ 8.6		16.3 $\pm$ 14.8
<i>(N)</i>	(125)	(573)	(527)	(249)		(975)

## Efficacy regarding bowel function

The mean BFI at study entry was 53.5 $\pm$  27.9 for the overall population (Table 3). As expected BFI at study entry was significantly higher in patients pre-treated with WHO-step 3 medication (65.3 $\pm$  23.0, n=571) compared with WHO-step 1 (31.8 $\pm$  26.4, n=141) and WHO-step 2 (47.7 $\pm$  27.7, n=625) medication ( $p$ <0.001).

The response rate with respect to bowel function during PR OXN treatment was 82.5% at last visit, indicating that bowel function during PR OXN treatment was evaluated as 'slightly better' to 'much better' for the majority of patients. Highest response was seen in the WHO-step 3 group (89.0%) and lower responses were seen in the WHO-step 2 and WHO-step 1 group (81.0% and 63.1% respectively).

In line with the response rate a significant and clinically relevant decrease ( $\Delta$  BFI (mean $\pm$  sd) -28.39  $\pm$  26.45;  $p$ <0.0001) in BFI was observed during PR OXN treatment compared to previous analgesic treatment between visit 1 and last visit for the overall group, with the largest (and clinically relevant) decrease in the WHO-step 3 subgroup and the lowest non clinically relevant decrease of 10.5 points in the WHO-step 1 subgroup ( $\Delta$  BFI (mean  $\pm$  sd) -10.5  $\pm$  20.86 for WHO-step 1 group; -24.6  $\pm$  26.20 for WHO-step 2 group and -36.87  $\pm$  24.78 for WHO-step 3 group). After 6 weeks of PR OXN treatment, the mean $\pm$  sd BFI values for the overall population, WHO-step 1 and WHO-step 2 groups

were below the constipation threshold of 28.8 and around that threshold for the WHO-step 3 group ( $30.33 \pm 19.48$ ) (Figure 2).

**Table 3.** Bowel function (BFI scores) over time per subgroup and overall

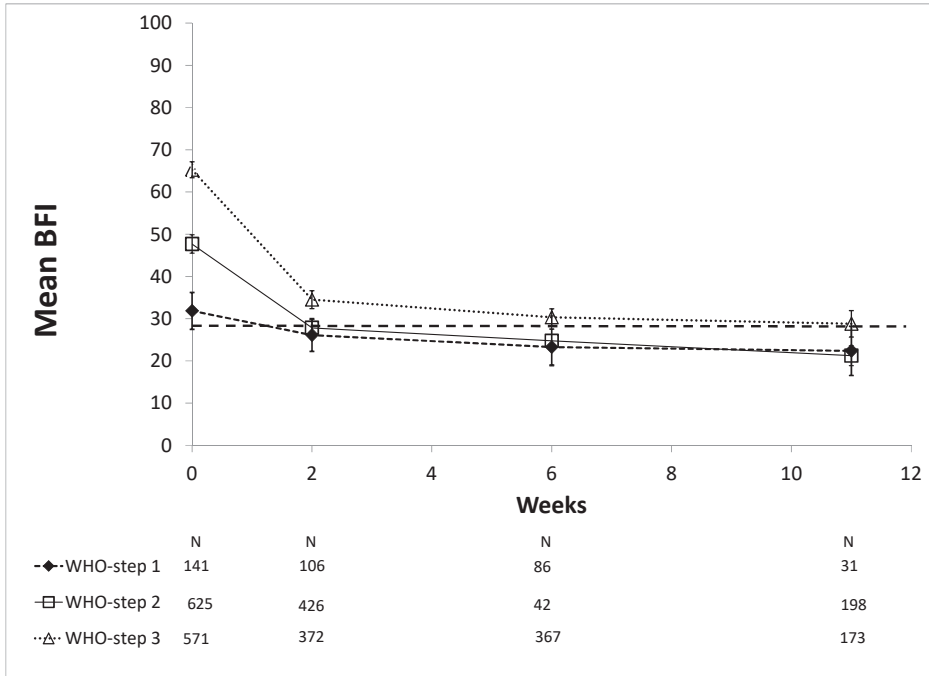
Bowel function (BFI score)	Previous WHO step analgesic			Bowel Function		Total N = 1338
	Step 1 N = 142	Step 2 N = 625	Step 3 N = 571	Non-constipated N=289	Constipated N=1048	
<b>Study start (visit 1)</b>						
Mean $\pm$ SD (N)	31.8 $\pm$ 26.5 (141)	47.7 $\pm$ 27.6 (625)	65.3 $\pm$ 23.0 (571)	10.4 $\pm$ 9.3 (289)	65.4 $\pm$ 17.8 (1048)	53.5 $\pm$ 27.9 (1337)
<b>Week 2<math>\pm</math>2</b>						
Mean $\pm$ SD (N)	26.1 $\pm$ 20.4 (106)	27.8 $\pm$ 20.5 (426)	34.5 $\pm$ 21.0 (372)	11.9 $\pm$ 15.4 (213)	35.9 $\pm$ 18.9 (690)	30.3 $\pm$ 20.9 (903)
<b>Week 6<math>\pm</math>2</b>						
Mean $\pm$ SD (N)	23.3 $\pm$ 20.1 (86)	24.7 $\pm$ 19.6 (427)	30.3 $\pm$ 19.5 (367)	11.6 $\pm$ 15.6 (168)	30.5 $\pm$ 18.9 (711)	26.9 $\pm$ 19.8 (879)
<b>Week 11<math>\pm</math>3</b>						
Mean $\pm$ SD (N)	22.4 $\pm$ 16.5 (31)	21.2 $\pm$ 17.0 (198)	28.8 $\pm$ 20.9 (173)	9.3 $\pm$ 9.6 (78)	28.2 $\pm$ 18.9 (324)	24.6 $\pm$ 19.1 (402)
<b>Week 17<math>\pm</math>3</b>						
Mean $\pm$ SD (N)	11.3 $\pm$ 14.9 (5)	26.9 $\pm$ 26.2 (22)	31.7 $\pm$ 23.1 (26)	13.6 $\pm$ 29.5 (11)	31.5 $\pm$ 21.5 (42)	27.8 $\pm$ 24.2 (53)
<b>Study End (Last visit)</b>						
Mean $\pm$ SD (N)	21.6 $\pm$ 18.9 (141)	23.0 $\pm$ 19.0 (625)	28.4 $\pm$ 19.9 (571)	10.7 $\pm$ 16.7 (288)	28.2 $\pm$ 19.7 (1048)	25.2 $\pm$ 19.6 (1337)

For patients with constipation at study entry (N=1048; BFI (mean  $\pm$  sd)  $65.40 \pm 17.81$ ) a significant and clinically relevant decrease (mean  $-36.40 \pm 22.90$ ;  $p < 0.0001$ ) in BFI was observed during PR OXN treatment between visit 1 and last visit. Analysis over time showed that already in the first 2 weeks of PR OXN treatment a fast and clinically relevant BFI reduction was observed (BFI (mean  $\pm$  sd)  $35.99 \pm 18.96$  (N=690)). After 11 weeks PR OXN treatment, the BFI (mean  $\pm$  sd) had further decreased to  $28.24 \pm 18.97$  (N=324) (Figure 3A).

For patients without constipation at study entry (n=289), the mean BFI remained well below 28.8 up to 17 weeks of PR OXN treatment (Figure 3A). Table 3 gives the actual BFI-values over time.

### Laxative use during the study

Despite the high level of constipation at study entry between visit 1 and visit 2 in the total population only 31.3% (419/1337) of patients used additional laxatives during the study and this additional laxative use was significantly higher in patients pretreated

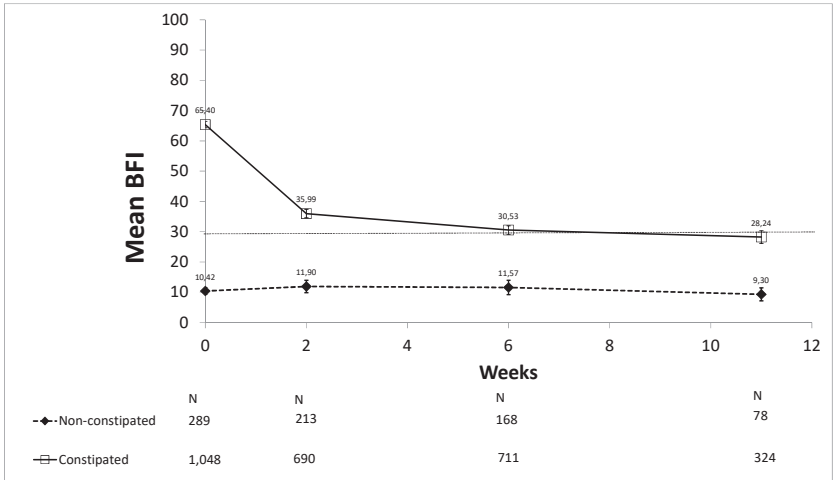


**Figure 2.** Bowel function measured by BFI over time for patients in WHO-step 1, WHO-step 2 and the WHO-step 3 groups (Full analysis-population)

Dashed line and closed diamonds represent the WHO-step 1 group, solid line and open squares represent the WHO-step 2 group and the dotted line and open triangles represent the WHO-step 3 group. The dotted line at BFI 28,8 represents the cut-off for constipation. Error bars represent the 95% confidence interval of the mean BFI. Patient numbers at weeks 0, 2, 6 and 11 are listed below the graph.

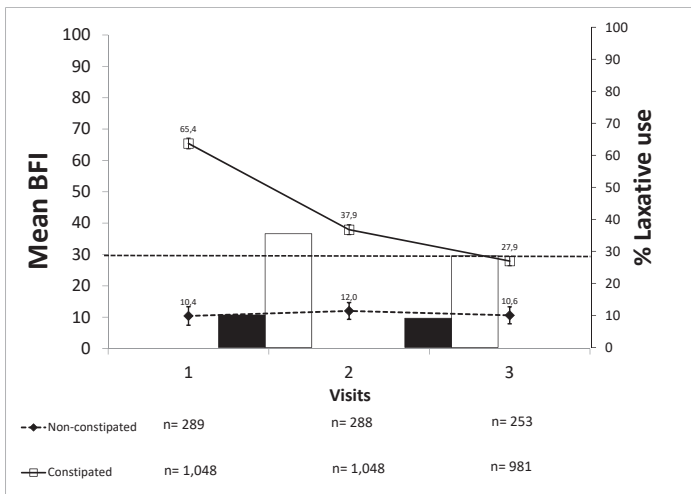
with WHO-step 3 medication (41.7%, 238/571) compared with patients pretreated with WHO-step 1 medication (20.4%, 29/241) and WHO-step 2 medication (24.3% 152/625;  $p < 0.001$ ). The percentage of patients using laxatives did not change significantly during the study for the WHO-step groups.

Looking at constipated patients versus non-constipated patients at study entry laxative use during the study was significantly higher in constipated than non-constipated patients (36.9% (387/1048) vs. 11.1% (32/289) respectively,  $p < 0.001$ ). Despite treatment with PR OXN, laxative use between visit 1 and visit 2 versus laxative use between visit 2 and visit 3 did not change significantly for non-constipated patients at study entry (10.1% to 9.1%), which is in line with the stable BFI. For patients with constipation at study entry a numerical but not statistically significant decrease in laxative use was seen (35.5% to 28.6%), which is in line with the improvement seen in the BFI (Figure 3B).



**Figure 3A.** Bowel function measured by BFI over time for constipated and non-constipated patients (FA population)

Dotted line and closed diamonds represent non-constipated patients (BFI<28.8) and the solid line and open squares represent constipated patients (BFI≥28.8). The line at BFI 28,8 represents the cut-off value between constipated and non-constipated patients. Error bars represent the 95% confidence interval of the mean BFI. Patient numbers at weeks 0, 2, 6 and 11 are listed below the graph.



**Figure 3B.** Bowel function measured by BFI per visit and laxative use for constipated patients and non-constipated patients (Full analysis population)

Dotted line and closed diamonds represents non-constipated patients (BFI<28.8) and the solid line and open squares represents constipated patients (BFI≥28.8). The line at BFI 28 represents the cut-off value between constipated and non-constipated patients. Error bars represent the 95% confidence interval of the mean BFI. Solid filled black bars represent the percentage of non-constipated patients using laxatives between visit 1 and 2 (29/288 (10.1%)) and between visit 2 and 3 (23/253 (9.1%)). Open bars represent the percentage of constipated patients using laxatives between visit 1 and 2 (372/1,048 (35.5%)) and between visit 2 and 3 (281/981 (28.6%)). Patient numbers at visit 1, 2 and 3 are listed below the graph.

## Efficacy regarding pain relief

The response rate regarding pain relief at last visit after PR OXN treatment was 84.5%, indicating that analgesic efficacy of PR OXN treatment was evaluated as 'slightly better', 'better' or 'much better' compared to the previous analgesic medication for the majority of patients. As expected responses were high in all groups, with a significantly lower response rate in the WHO-step 3 group (77.1%,  $p < 0.001$ ) compared with response rates of 91.5% and 89.8% in the WHO-step 1 and WHO-step 2 groups respectively. Looking more closely at subjects with and without constipation, at visit 2 and visit 3, response was significantly higher in the non-constipated subgroup (85.8% at visit 2 and 92.1% at visit 3) than in the constipated subgroup at visit 2 and visit 3 (80.2 ( $p = 0.033$ ) and 85.7% ( $p = 0.006$ ) respectively).

Table 4 gives the actual pain intensity scores over time.

**Table 4.** Pain intensity scores over time per subgroup and overall.

Pain intensity score (NRS)	Previous WHO step analgesic			Bowel Function		Total N = 1338
	Step 1 N = 142	Step 2 N = 625	Step 3 N = 571	Non-constipated N=289	Constipated N=1048	
<b>Study start (visit 1)</b>						
Mean $\pm$ SD (N)	7.3 $\pm$ 1.3 (141)	7.7 $\pm$ 1.1 (625)	6.7 $\pm$ 2.0 (571)	7.6 $\pm$ 1.3 (289)	7.2 $\pm$ 1.7 (1048)	7.2 $\pm$ 1.7 (1337)
<b>Week 2<math>\pm</math>2</b>						
Mean $\pm$ SD (N)	4.3 $\pm$ 2.1 (106)	4.7 $\pm$ 1.9 (426)	4.7 $\pm$ 2.0 (372)	4.2 $\pm$ 2.1 (213)	4.8 $\pm$ 1.8 (690)	4.7 $\pm$ 1.9 (904)
<b>Week 6<math>\pm</math>2</b>						
Mean $\pm$ SD (N)	3.9 $\pm$ 2.1 (86)	4.0 $\pm$ 1.9 (427)	4.2 $\pm$ 1.7 (368)	3.7 $\pm$ 2.0 (168)	4.2 $\pm$ 1.8 (712)	4.1 $\pm$ 1.8 (881)
<b>Week 11<math>\pm</math>3</b>						
Mean $\pm$ SD (N)	4.2 $\pm$ 2.4 (31)	3.5 $\pm$ 1.6 (198)	4.3 $\pm$ 1.9 (173)	3.4 $\pm$ 1.8 (78)	4.0 $\pm$ 1.8 (324)	3.9 $\pm$ 1.8 (402)
<b>Week 17<math>\pm</math>3</b>						
Mean $\pm$ SD (N)	5.4 $\pm$ 0.9 (5)	3.4 $\pm$ 1.5 (22)	4.3 $\pm$ 1.6 (26)	4.5 $\pm$ 1.6 (11)	4.0 $\pm$ 1.6 (42)	4.1 $\pm$ 1.6 (53)
<b>Study End (Last visit)</b>						
Mean $\pm$ SD (N)	3.8 $\pm$ 2.2 (141)	3.7 $\pm$ 1.9 (625)	4.1 $\pm$ 1.9 (571)	3.5 $\pm$ 2.1 (288)	4.0 $\pm$ 1.9 (1048)	3.9 $\pm$ 1.9 (1337)

## Quality of life

Patients reported that during treatment with PR OXN all aspects of quality of life (QoL) improved, resulting in a significant increase of  $0.31 \pm 0.26$  (95% CI [0.30,0.32]) in the EQ-D5 score from first to last visit. QoL improved significantly in all three WHO-step groups

with a significantly larger increase in both WHO-step 1 and WHO-step 2 groups (both  $0.34 \pm 0.26$ ) compared to the WHO-step 3 group ( $0.27 \pm 0.26$ ;  $p < 0.0001$ ).

Similarly, the self-reported EQ-5D VAS health scores showed an increase of  $16.5 \pm 26.8$  (95% CI 15.0,18.0) between the first ( $41.2 \pm 22.0$ ) and last visit ( $58.2 \pm 21.7$ ). The improvement was significantly larger for the WHO-step 2 group ( $19.6 \pm 27.5$ ) compared to the WHO-step 1 group ( $17.4 \pm 27.0$ ) and the WHO-step 3 group ( $13.0 \pm 25.5$ ;  $p = 0.0002$ ).

QoL also improved significantly in both bowel function groups, with a statistically significant larger increase in non-constipated patients ( $0.38 \pm 0.27$ ) versus constipated patients ( $0.29 \pm 0.25$ ;  $p < 0.0001$ ). No statistically significant differences are seen in changes from baseline to last visit in EQ-5D VAS health scores between non-constipated ( $18.2 \pm 32.0$ ) and constipated groups ( $16.1 \pm 25.3$ ).

## Safety

Overall, 4.8% of the patients in the safety population reported at least one adverse drug reaction (ADR) during OXN treatment (77 ADRs reported by 66 out of 1369 patients). The most frequently reported ADRs were nausea (1.2%), constipation (0.9%), drowsiness (0.5%), vertigo/dizziness (0.5%) and somnolence (0.3%). Most ADRs documented as mild (36.9%) or moderate (44.6%) mainly affecting the gastrointestinal system and the central nervous system (Table 5).

**Table 5.** Number of patients with at least one adverse drug reaction, severity and relation to study medication of reported adverse drug reactions (safety population)

	<b>Total N = 1369</b>
Any Adverse Drug Reaction	4.8% (66/1369)
Maximal ADR Severity Reported, % (n/N)	
Mild	36.9% (24/65)
Moderate	44.6% (29/65)
Severe	18.5% (12/65)
Missing	1
Maximal ADR Relation Reported, % (n/N)	
Not related	3.3% (2/60)
Possibly related	28.3% (17/60)
Probably related	51.7% (31/60)
Definitely related	16.7% (10/60)
Missing	6

ADR, adverse drug reaction

Twelve ADR (18.5%) were severe and mainly affected the gastrointestinal system (nausea and constipation). No additional ADR compared to the ADR mentioned in the

SmPC were reported. No serious ADRs were documented. Twenty-eight patients (2.2 %) reported stopping the study because of an adverse drug reaction. The incidence of drug related adverse events was comparable between analgesic pretreatment-groups (WHO-step 1, WHO-step 2 and WHO-step 3) as well as between constipated and non-constipated patients.

## DISCUSSION

The present study showed that the majority of patients in the total population (78.4%) and in all WHO-step groups experienced symptoms of constipation as defined by a  $BFI \geq 28.8$  (50.4%, 72.8% and 91.4% for WHO-step 1, WHO-step 2 and WHO-step 3 respectively)<sup>33</sup>. It was shown that significantly more patients with symptoms of constipation at study entry were older and of female gender, both factors that are known to be associated with constipation and patients with pain are less mobile which could also have contributed to constipation<sup>9-11</sup>. Moreover, it is possible that there is a bias in the percentage of constipated patients in this observation as in Belgium PR OXN was marketed especially for patients with a BFI above 30. Also in literature it has been demonstrated that treatment with WHO-step 1 and WHO-step 2 analgesics, like NSAIDs, codeine and tramadol are strongly associated with occurrence of constipation. This might have contributed to the high percentage of constipated patients in the WHO-step 1 and WHO-step 2 groups, together with the other factors that are associated with constipation that are present in the study population<sup>34-37</sup>.

Already after 2 weeks of PR OXN treatment a clinically relevant improvement of bowel function (defined by a reduction in BFI of 12 points or more) was observed in the overall population and in the WHO-step 2 and WHO-step 3 groups. Mean BFI dropped below 28.8 after 6 weeks of PR OXN treatment for the overall population and the WHO-step 1 and WHO-step 2 groups. In the WHO-step 3 group mean BFI reached 28.8 after 11 weeks of PR OXN treatment. The observed reduction in BFI for all groups was maintained over time. These results indicate that during the observation bowel function can restore over time irrespective of the previous analgesic treatment, despite initiation of the opioid PR OXN. The reduction in BFI is in line with reduction of BFI reported in previous observational studies with PR OXN for patients with neuropathic pain<sup>28</sup>, constipated patients with non-malignant pain<sup>29</sup> and patients with severe pain<sup>30</sup>. In this observation also patients switching from WHO-step 1 and WHO-step 2 medication, as well as patients without constipation at start of the observation were included, which is in contrast to previous studies, in which patients already experienced OIC or were switched from WHO-step 3 medication to PR OXN.

When looking more closely at constipated patients at study entry (irrespective of previous analgesic treatment), it was shown that treatment with PR OXN led to a clinically relevant improved bowel function already in the first two weeks of PR OXN treatment and the improvement was maintained over time. After 17 weeks, BFI was close to the threshold of 28.8 showing that bowel function was almost restored to normal values despite the treatment with the opioid PR OXN. Interestingly, for patients not constipated at study entry the BFI remained below 28.8 even during PR OXN treatment up to 17 weeks. This indicates that treating pain adequately with strong opioids in non-constipated patients normal bowel function is maintained despite the initiation of the opioid PR OXN, even in patients stepping-up from non-opioid treatment. This study adds to the evidence found in previous studies with PR OXN which have also shown that switching non-constipated patients to PR OXN maintained their bowel function in a more controlled study setting (one clinical trial and one prospective open-label study with a blinded endpoint)<sup>38,39</sup>.

Importantly, the reduction in BFI cannot be explained by increased use of laxatives. The percentage of patients using laxatives at subsequent visits in the overall population and all subgroups remains stable indicating that the clinically relevant improvement in bowel function during PR OXN treatment cannot be attributed to an increased use of laxatives. This adds to the evidence that PR OXN is a pathophysiological treatment for OIC targeting the underlying cause of OIC and not a symptomatic treatment for OIC as is the case with laxatives<sup>40,41</sup>. These results suggest that for patients with pre-existing risk-factors for constipation (like older age, female gender and immobility) as well as for patients with pre-existing symptoms of constipation, PR OXN might be a valuable option to treat severe pain, whilst maintaining or even restoring normal bowel function.

In Belgium patients have a co-payment for laxatives which could have led to a lower level of patients using laxatives at start of the observation. The percentage of patients using laxatives during the observation is also low, 31.3% of patients used laxatives during the observation. PR OXN has been shown to improve and prevent symptoms of constipation with reduced laxative use compared with prolonged release oxycodone. Treatment with PR OXN and co-payment for laxatives in Belgium might have led to the low level of laxative use in this observation.

This study also showed that pain relief during PR OXN treatment was “slightly better”, “better” or “much better” for the vast majority of patients with severe pain as compared to the previous analgesic treatment. Response rate with respect to pain relief (proportion of patients with pain relief that was “slightly better”, “better” or “much better”) was significantly lower in WHO-step 3 pretreated patients (77.1%) compared with WHO-step 1 and WHO-step 2 pretreated patients (91.5% and 89.9%, respectively). This was as expected since treatment was stepped-up for patients pretreated with WHO-step 1 and or WHO-step 2 analgesics to a WHO-step 3 analgesic. Counter-intuitively, there were no



significant differences in mean PR OXN dose between the subgroups, which might contribute to a lower efficacy for pain relief in the WHO-step 3 subgroup. Patients pretreated with WHO-step 3 analgesics treatment were switched to another WHO-step 3 analgesic with the addition of naloxone and all randomized clinical trials and observational trials so far have shown that the addition of naloxone to oxycodone did not influence pain relief compared with oxycodone<sup>20-27</sup>. As the majority of patients in the WHO-step 3 pretreated group were switched to PR OXN due to side effects of the WHO-step 3 pretreatment (86.2%), physicians might have been more conservative in titrating the PR OXN dose.

We observed that there was a small but significant difference in pain relief during PR OXN treatment when looking at constipated versus non-constipated patients at study entry favoring non-constipated patients. This might be explained by the fact that 49.8% of constipated patients were pretreated with WHO-step 3 medication and these WHO-step 3 pretreated patients had a significantly lower response rate with respect to pain relief (77.1%) compared with WHO-step 1 and WHO-step 2 pretreated patients (91.5% and 89.8% respectively). Logistic regression analyses with adjustment for age, gender, type of pain and constipation level, showed that the previously used WHO step analgesic is a statistically significant predictor for response to pain relief at last visit.

In the present observational study, patients reported a significant increase in their self-perception of quality of life compared to previous analgesic treatment. The improvement in QoL was significantly higher in patients previously treated with WHO-step 1 and 2 analgesics. This might be expected taking into account that patients previously treated with WHO-step 3 analgesics had significantly less pain relief during the study compared to the other WHO-step subgroups. Improvement in QoL also significantly improved in constipated patients and non-constipated patients, with the improvement being significantly higher in non-constipated patients compared with constipated patients.

However, both the significant increase in pain relief and the significant decrease in OIC could have contributed to the increase in QoL in this study. It has been consistently reported that pain has an inverse correlation between the extent of its relief and the associated QoL<sup>42</sup> and that OIC has a negative impacts on QoL too<sup>1,10,12</sup>.

Unfortunately, with the current study design it is not possible to distinguish between the contribution of improved bowel function and pain relief to the improvement of QoL. Further studies are warranted to investigate the impact of OIC on QoL of pain patients taking into account their level of pain control as well as pain medication used.

The nature of the adverse drug reactions reported during the study are among those documented for oxycodone/naloxone as outlined in the SmPC. The incidence of drug related adverse events was comparable between subgroups of patients. The frequency of ADR reported in this study are lower than reported in the SmPC. Despite the fact that at each study visit the physicians had to actively answer a question about the oc-

currence of adverse drug reactions in the period before the study visit as a reminder to report all ADRs, we suspect that there is under reporting of ADRs. Unfortunately, this is a well-known and common problem, especially in observational studies<sup>43</sup>. Moreover, the adverse drug reaction profile seen with oxycodone/naloxone is very similar to the profile of oxycodone and oxycodone is a well-known compound to physicians. Therefore the expectations of the physician regarding ADRs with oxycodone/naloxone might have also led to underreporting of ADRs in this observation.

Limitations of the present study include its prospective observational open-label design and the lack of a control arm not using PR OXN. However, the strict in- and exclusion criteria seen in randomized controlled clinical trials were not used in this real-life non-interventional prospective observational study, resulting in findings that are applicable to real-life patient populations.

## CONCLUSIONS

The results of this real-life non-interventional prospective observational study performed in daily clinical practice in Belgium show that patients with severe pain report a significant and clinically relevant improvement of bowel function as well as an improvement of QoL compared to the previous WHO analgesic treatment during PR OXN treatment. The majority of patients (84.5%) with severe pain switching from their preceding analgesic treatment to PR OXN indicate the efficacy of PR OXN regarding pain relief as 'slightly better', 'better' or 'much better' compared to the previous analgesic medication at last visit.

More interesting, constipated subjects showed a significant and clinically relevant improvement in bowel function (BFI) over time, while laxative use numerically decreased.

In non-constipated subjects, the BFI remains well below the threshold value for normal bowel function (28.8) whilst laxative use remains low (~10%), showing a prevention of constipation despite the use of an opioid. This confirms that treatment with PR OXN improves bowel function in constipated subjects and might maintain bowel function in non-constipated patients even during treatment with opioid analgesics, reflecting the local action of opioids in the gut and the pathophysiological action of naloxone (in PR OXN) on bowel function.

All adverse drug reactions observed were well-known opioid-related AEs raising no additional safety concerns.

## **TRANSPARENCY**

### **Declaration of funding**

This study was designed by Mundipharma Pharmaceuticals BV and Mundipharma Comm. VA, and conducted by qualified investigators under the sponsorship of Mundipharma Pharmaceuticals BV and Mundipharma Comm. VA. Data were gathered by the sponsor and evaluated jointly by the authors and the sponsor. There is no financial interest linked to the preparation, scientific advice and authorship of the article for the authors. No grants, equipment or drugs were supplied by the sponsor. F.J.P.M. Huygen and I. Mancini provided scientific advice to Mundipharma Pharmaceuticals BV. H. Prenen participated as investigator in the study. All authors were involved in the development, writing, critical reviewing and approval of this manuscript.

### **Declaration of financial/other relationships**

I. Mancini, H. Prenen and F.J.P.M. Huygen have nothing to disclose.

Y.J.B. van Megen and G. Koopmans-Klein report personal fees from Mundipharma Pharmaceuticals BV, during the conduct of the study and personal fees from Mundipharma Pharmaceuticals BV, outside the submitted work. J. Van Op den bosch reports personal fees from Mundipharma Comm. VA at time of study conduct and article drafting and personal fees from Mundipharma Comm. VA outside the submitted work.

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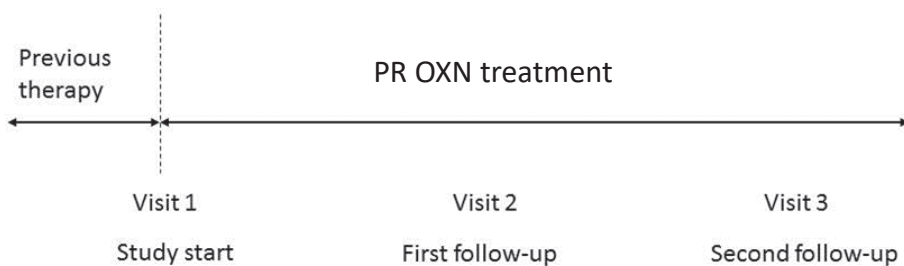
## REFERENCES

1. Breivik H, Collett B, Ventafridda V, Cohen R, Gallacher D. Survey of chronic pain in Europe: prevalence, impact on daily life, and treatment. *Eur J Pain* 2006 May;10(4):287-333.
2. Blyth FM, March LM, Brnabic AJM, Cousins MJ. Chronic pain and frequent use of health care. *Pain* 2004(111):51-58.
3. WHO. Cancer pain relief, with a guide to opioid availability. WHO guideline 1996 1996;Second edition:13-15.
4. Eisenberg E, McNicol ED, Carr DB. Efficacy and safety of opioid agonists in the treatment of neuropathic pain of nonmalignant origin: systematic review and meta-analysis of randomized controlled trials. *JAMA* 2005 Jun 22;293(24):3043-52.
5. Chou R, Clark E, Helfand M. Comparative efficacy and safety of long-acting oral opioids for chronic non-cancer pain: a systematic review. *J Pain Symptom Manage* 2003 Nov;26(5):1026-48.
6. Allan L, Hays H, Jensen NH, de Waroux BL, Bolt M, Donald R, et al. Randomised crossover trial of transdermal fentanyl and sustained release oral morphine for treating chronic non-cancer pain. *BMJ* 2001 May 12;322(7295):1154-8.
7. Drewes AM, Jensen RD, Nielsen LM, Droney J, Christrup LL, Arendt-Nielsen L, et al. Differences between opioids: pharmacological, experimental, clinical and economical perspectives. *Br J Clin Pharmacol* 2012;75(1):60-78.
8. Coluzzi F, Pappagallo M, National Initiative on Pain C. Opioid therapy for chronic noncancer pain: practice guidelines for initiation and maintenance of therapy. *Minerva Anestesiol* 2005 Jul-Aug;71(7-8):425-33.
9. Brock C, Olesen SS, Olesen AE, Frokjaer JB, Andresen T, Drewes AM. Opioid-induced bowel dysfunction: pathophysiology and management. *Drugs* 2012 Oct 1;72(14):1847-65.
10. Bell TJ, Panchal SJ, Miaskowski C, Bolge SC, Milanova T, Williamson R. The prevalence, severity, and impact of opioid-induced bowel dysfunction: results of a US and European Patient Survey (PROBE 1). *Pain Med* 2009 Jan;10(1):35-42.
11. Diego L, Atayee R, Helmons P, Hsiao G, von Gunten CF. Novel opioid antagonists for opioid-induced bowel dysfunction. *Expert Opin Investig Drugs* 2011 Aug;20(8):1047-56.
12. Penning-van Beest FJA, Haak=van den P, Klok RM, Prevooy YFDM, Peet=van der DL, Herings RMC. Quality of life in relation to constipation among opioid users. *J Med Econ* 2010;13(1):129-35.
13. Coyne KS, LoCasale RJ, Datto CJ, Sexton CC, Yeomans K, Tack J. Opioid-induced constipation in patients with chronic noncancer pain in the USA, Canada, Germany, and the UK: descriptive analysis of baseline patient-reported outcomes and retrospective chart review. *ClinicoEconomics and outcomes research : CEOR* 2014;6:269-81.
14. Abramowitz L, Beziaud N, Labreze L, Giardina V, Causse C, Chuberre B, et al. 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* 2013 Dec;16(12):1423-33.
15. Panchal SJ, Muller-Schwefe P, Wurzelmann JI. Opioid-induced bowel dysfunction: prevalence, pathophysiology and burden. *Int J Clin Pract* 2007 Jul;61(7):1181-7.
16. McNicol E, Horowicz-Mehler N, Fisk RA, Bennett K, Gialeli-Goudas M, Chew PW, et al. Management of opioid side effects in cancer-related and chronic noncancer pain: a systematic review. *J Pain* 2003 Jun;4(5):231-56.
17. Pappagallo M. Incidence, prevalence, and management of opioid bowel dysfunction. *Am J Surg* 2001 Nov;182(5A Suppl):115-185.

18. Mancini IL, Bruera E. Constipation in advanced cancer patients. *Support Care Cancer* 1998;6:356-64.
19. Smith K, Hopp M, Mundin G, Bond S, Bailey P, Woodward J, et al. Low absolute bioavailability of oral naloxone in healthy subjects. *Int J Clin Pharmacol Ther* 2012 May;50(5):360-7.
20. Vondrackova D, Leyendecker P, Meissner W, Hopp M, Szombati I, Hermanns K, et al. Analgesic efficacy and safety of oxycodone in combination with naloxone as prolonged release tablets in patients with moderate to severe chronic pain. *J Pain* 2008 Dec;9(12):1144-54.
21. Simpson K, Leyendecker P, Hopp M, Muller-Lissner S, Lowenstein O, De Andres J, et al. 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* 2008 Dec;24(12):3503-12.
22. Sandner-Kiesling A, Leyendecker P, Hopp M, Tarau L, Lejcko J, Meissner W, et al. Long-term efficacy and safety of combined prolonged-release oxycodone and naloxone in the management of non-cancer chronic pain. *Int J Clin Pract* 2010 May;64(6):763-74.
23. Meissner W, Leyendecker P, Mueller-Lissner S, Nadstawek J, Hopp M, Ruckes C, et al. A randomised controlled trial with prolonged-release oral oxycodone and naloxone to prevent and reverse opioid-induced constipation. *Eur J Pain* 2009 Jan;13(1):56-64.
24. Lowenstein O, Leyendecker P, Hopp M, Schutter U, Rogers PD, Uhl R, et al. 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* 2009 Mar;10(4):531-43.
25. Lowenstein O, Leyendecker P, Lux EA, Blagden M, Simpson KH, Hopp M, et al. Efficacy and safety of combined prolonged-release oxycodone and naloxone in the management of moderate/severe chronic non-malignant pain: results of a prospectively designed pooled analysis of two randomised, double-blind clinical trials. *BMC Clin Pharmacol* 2010;10:12.
26. Ahmedzai SH, Nauck F, Bar-Sela G, Bosse B, Leyendecker P, Hopp M. A randomized, double-blind, active-controlled, double-dummy, parallel-group study to determine the safety and efficacy of oxycodone/naloxone prolonged-release tablets in patients with moderate/severe, chronic cancer pain. *Palliat Med* 2012 Jan;26(1):50-60.
27. Kuusniemi K, Zollner J, Sjoval S, Huhtala J, Karjalainen P, Kokki M, et al. Prolonged-release oxycodone/naloxone in postoperative pain management: from a randomized clinical trial to usual clinical practice. *J Int Med Res* 2012;40(5):1775-93.
28. Hermanns K, Junker U, Nolte T. Prolonged-release oxycodone/naloxone in the treatment of neuropathic pain - results from a large observational study. *Expert Opin Pharmacother* 2012 Feb;13(3):299-311.
29. Gatti A, Casali M, Lazzari M, Tufaro G, Gafforio P, Silvestri C, et al. Prolonged-release oxycodone/naloxone in nonmalignant pain: single-center study in patients with constipation. *Adv Ther* 2013 Jan;30(1):41-59.
30. Schutter U, Grunert S, Meyer C, Schmidt T, Nolte T. Innovative pain therapy with a fixed combination of prolonged-release oxycodone/naloxone: a large observational study under conditions of daily practice. *Curr Med Res Opin* 2010 Jun;26(6):1377-87.
31. Rentz AM, Yu R, Muller-Lissner S, Leyendecker P. Validation of the Bowel Function Index to detect clinically meaningful changes in opioid-induced constipation. *J Med Econ* 2009;12(4):371-83.
32. Rentz AM, van Hanswijck de Jonge P, Leyendecker P, Hopp M. Observational, nonintervention, multicenter study for validation of the Bowel Function Index for constipation in European countries. *Curr Med Res Opin* 2011 Jan;27(1):35-44.

33. Ueberall MA, Muller-Lissner S, Buschmann-Kramm C, Bosse B. The Bowel Function Index for evaluating constipation in pain patients: definition of a reference range for a non-constipated population of pain patients. *J Int Med Res* 2011;39(1):41-50.
34. Chang JY, Locke GR, Schleck CD, Zinsmeister AR, Talley NJ. Risk factors for chronic constipation and a possible role of analgesics. *Neurogastroenterol Motil* 2007 Nov;19(11):905-11.
35. Fosnes GS, Lydersen S, Farup PG. Constipation and diarrhoea - common adverse drug reactions? A cross sectional study in the general population. *BMC Clin Pharmacol* 2011;11(2):2.
36. Langley PC, Patkar AD, Boswell KA, Benson CJ, Schein JR. Adverse event profile of tramadol in recent clinical studies of chronic osteoarthritis pain. *Curr Med Res Opin* 2010 Jan;26(1):239-51.
37. Clark K, Lam LT, Agar M, Chye R, Currow DC. The impact of opioids, anticholinergic medications and disease progression on the prescription of laxatives in hospitalized palliative care patients: a retrospective analysis. *Palliat Med* 2010 Jun;24(4):410-8.
38. van Dongen VC, Vanelderden PJ, Koopmans-Klein G, van Megen YJ, Van Zundert J, Huygen FJ. Patient preference with respect to QoL and reduction in opioid-induced constipation (OIC) after treatment with prolonged-release (PR) oxycodone/naloxone compared with previous analgesic therapy [PREFER study]. *Int J Clin Pract* 2014 Nov;68(11):1364-75.
39. Ueberall MA, Mueller-Schwefe GH. Safety and efficacy of oxycodone/naloxone vs. oxycodone vs. morphine for the treatment of chronic low back pain: results of a 12 week prospective, randomized, open-label blinded endpoint streamlined study with prolonged-release preparations. *Curr Med Res Opin* 2015;31(7):1413-29.
40. Müller-Lissner S. Opioid-induced Constipation - Mechanisms, Relevance and Management. *European gastroenterology & hepatology review* 2010:54-57.
41. Leppert W. The role of opioid receptor antagonists in the treatment of opioid-induced constipation: a review. *Adv Ther* 2010 Oct;27(10):714-30.
42. McCarberg BH, Nicholson BD, Todd KH, Palmer T, Penles L. The impact of pain on quality of life and the unmet needs of pain management: results from pain sufferers and physicians participating in an Internet survey. *Am J Ther* 2008 Jul-Aug;15(4):312-20.
43. Khan SA, Goyal C, Chandel C and Rafi M. Knowledge, attitudes, and practice of doctors to adverse drug reaction reporting in a teaching hospital in India: An observational study. *J Nat Sci Biol Med.* 2013 Jan-Jun; 4(1): 191–196.

**SUPPLEMENTARY FIGURES**



Study Visit	Visit 1	Visit 2	Visit 3
	Start	First follow-up	Second follow-up
Inclusion/exclusion criteria	X		
Demography	X		
Medical history	X		
Current medication use	X		
Efficacy evaluation (pain relief) <sup>a</sup>		X	X
Pain (NRS) score (0-10)	X <sup>a</sup>	X	X
Bowel Function Index <sup>b</sup>	X <sup>a</sup>	X	X
Efficacy evaluation (bowel function) <sup>a</sup>		X	X
Laxative use <sup>c</sup>		X	X
Concomitant therapies		X	X
Analgesic rescue medication <sup>d</sup>		X	X
Adverse Drug Reactions		X	X
EQ-5D	X <sup>e</sup>	X <sup>f</sup>	X
PR OXN dispensation	X	X	X <sup>g</sup>

- a. efficacy of treatment, 7 categories (i.e. much worse, worse, slightly worse, same, slightly better, better, much better)
- b. patients assessment of difficulty of bowel movements, feeling of incomplete bowel evacuation, and personal judgement of constipation over the past 7 days.
- c. laxative use to be recorded by physician (yes/no, if yes: continuously, intermittently or rarely)
- d. record the use of analgesic rescue medication (yes/no)
- e. assessments related to use of previous analgesic medication (step 1, step 2 or step 3)
- f. only in case of discontinuation at Visit 2
- g. at the discretion of the physician

**Supplementary Figure 1.** Study diagram and outline of study procedures