# Treatment with Prolonged Release Oxycodone/Naloxone improves pain relief and Opioid Induced Constipation compared with Prolonged Release Oxycodone in patients with chronic severe pain and laxative-refractory constipation

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## ABSTRACT

### Purpose

Laxative-refractory OIC (defined as opioid-induced constipation despite using 2 laxatives with a different mechanism of action (based on the Anatomical Therapeutic Chemical (ATC) Classification System level 4 term, e.g. contact laxatives, osmotically acting laxatives, softeners/emollients, enema's and others)) has a great impact on the treatment and quality of life (QoL) of patients with severe chronic pain. This non-interventional observational, real-life study in Belgium investigates the efficacy of prolonged release oxycodone/naloxone combination (PR OXN) treatment regarding pain relief and OIC, compared to previous prolonged release oxycodone (PR OXY) treatment for laxative-refractory OIC patients in daily clinical practice.

### Methods

Laxative-refractory OIC patients with severe chronic pain were treated with PR OXN for 12 weeks (3 visits). Pain relief (numerical rating scale [NRS]) and OIC (Bowel Function Index [BFI]) were evaluated at each visit. A responder was defined as a patient who had a) no worsening of pain at last visit compared to visit 1, or an NRS ≤ 4 at visit 3/last visit, as well as b) a reduction in BFI ≥ 12 units at visit3/last visit compared to visit 1, or c) a BFI ≤28.8 at visit 3/last visit.

### Findings

68 laxative-refractory OIC patients with severe chronic pain were treated during 91 days with PR OXN (median daily dose 20 mg). Treatment with PR OXN resulted in a significant and clinically relevant decrease of pain with 2.1 units ($p<0.001$, 95% CI: 1.66, 2.54) and of BFI with 48.5 units ($p<00.001$; 95% CI: 44.4, 52.7) compared to PR OXY treatment, while use of laxatives was significantly reduced ($p<0.001$). 95.1% of patients was a responder and QoL (EQ-5D) improved significantly. Adverse events were opioid related and PR OXN treatment was well tolerated.

### Implications

Treatment with PR OXN results in a significant and clinically relevant reduction of OIC compared to previous PR OXY treatment for patients with severe chronic pain and laxative-refractory OIC. Treatment with PR OXN also resulted in a significant improvement in pain relief and quality of life.

### Clinical Trial Registry number

ClinicalTrials.gov identifier: NCT01710917

## INTRODUCTION

Opioids are widely used for treatment of patients with severe chronic pain. However, adverse drug reactions associated with the use of opioids, particularly opioid-induced bowel dysfunction (OIBD), can be very problematic and severely affect quality of life[1]. Opioid-induced constipation (OIC) is the most distressing lead symptom of OIBD and occurs in approximately 40% of opioid-treated patients[2, 3]. In contrast to opioid-related adverse effects mediated through the central opioid receptors, occurring at the start of the treatment and usually decreasing rapidly, OIC is mediated through intestinal opioid receptors, often persisting throughout opioid treatment without diminishing in intensity[4]. OIC is the most troublesome opioid-related side effect reported by patients, resulting in reduction or discontinuation of opioid treatment in a third of opioid-treated patients[1]. Laxatives are the most common drugs used for relieving OIC. However, since laxatives do not address the underlying mechanisms of OIC they are insufficiently effective in the majority of patients suffering from OIC[5, 6] . Moreover, there are no direct comparative data on different laxatives in the prevention or treatment of OIC, resulting in a lack of generally accepted guidelines on laxative use in OIC[6].

A strategy to minimize or prevent OIC while maintaining analgesic efficacy is blocking intestinal opioid receptors while allowing the activation of central opioid receptors[6]. To this end, a prolonged release tablet consisting of oxycodone and naloxone (PR OXN) in a 2:1 ratio has been developed. Oxycodone has been shown to be an effective analgesic in different types of pain[7]. Naloxone is an opioid receptor antagonist with low systemic bioavailability (<3%) primarily used as an injectable solution for treatment of opioid overdose by its antagonizing effect on central opioid receptors. When administered orally, naloxone antagonizes the opioid receptors in the gut wall, thereby counteracting OIC, while its extensive first pass hepatic metabolism ensures the lack of antagonist effect on the central analgesic effect of oxycodone[8].

Several randomized controlled studies demonstrated comparable analgesic efficacy of PR OXN and prolonged release oxycodone (PR OXY) with a significant and clinically relevant improvement in OIC of PR OXN compared to PR OXY in different types of pain even after long-term treatment[9-15]. The frequency of adverse events was similar between PR OXN and PR OXY treatment. This has been confirmed in a daily clinical practice in Germany for patients with a wide variety of pain etiologies[16].

PR OXN is indicated for the treatment of severe pain which can only be adequately managed with opioid analgesics. In Belgium reimbursement for PR OXN is strictly limited to patients who have been treated with PR OXY for at least the last 30 days prior to PR OXN treatment and who suffer from laxative-refractory OIC (defined as OIC despite the use of at least 2 laxatives with different mechanisms of action (based on the Anatomical Therapeutic Chemical (ATC) Classification System level 4 term, e.g. contact laxatives,

osmotically acting laxatives, softeners/emollients, enema's and others; level 4 ATC term) during previous PR OXY treatment.

This study was requested by the Belgian reimbursement authorities to investigate PR OXN efficacy regarding both pain relief and OIC in chronic pain patients eligible for PR OXN reimbursement in Belgium in real-life. Besides evaluation of efficacy regarding pain relief and OIC use of laxatives and analgesic rescue medication, quality of life and safety during PR OXN treatment compared to the previous PR OXY treatment were also evaluated.

## METHODS

### Study design

This non-interventional, observational, real-life study was designed to evaluate the pain relief and OIC of the PR OXN treatment in daily practice in patients with chronic severe pain compared to previous PR OXY treatment. PR OXN treatment started at visit 1. The study was performed with electronic Case Record Forms (eCRF). All parameters collected at visit 1 reflected the PR OXY treatment. Evaluations were performed during 2 follow up visits. Visit 2 was scheduled after PR OXN dose titration and visit 3 was scheduled at least 12 weeks after visit 1.

This study was conducted in accordance with Belgian and European health law and controlled drug regulations.

### Patients

Patients enrolled in this study met the reimbursement conditions for PR OXN in Belgium as well as the summary of product characteristics (SPC) for PR OXN. In Belgium patients are eligible for reimbursement if they meet the following conditions:

a) all patients had to be ≥ 18 years, with a documented history of severe pain requiring around-the-clock opioid therapy, treated with PR OXY during at least 30 days with insufficient pain relief and/or unacceptable side effects AND b) all patients had to be suffering from OIC (Bowel Function Index [BFI] ≥ 28.8, see section methods) despite the use of at least 2 laxatives with different mechanisms of action (level 4 ATC term) during the previous PR OXY treatment.

Patients were excluded from the study if any of the following criteria based on the SPC were met: any history of hypersensitivity to oxycodone, naloxone, related products or other ingredients; active alcohol or drug abuse and/or history of opioid abuse; patients who participated in a clinical research study involving a new chemical entity or an experimental drug within 30 days of study entry; surgery completed prior to the start of the study, or planned surgery during the study that would influence pain or bowel func-

tion; patients who had taken naloxone □30 days prior to the start of the study; patients suffering from diarrhoea and/or opioid withdrawal; patients with any situation in which opioids were contra-indicated; patients suffering from severe respiratory depression with hypoxia and/or hypercapnia, severe obstructive pulmonary disease, cor pulmonale, severe bronchial asthma, non-opioid induced paralytic ileus, moderate to severe liver function impairments, and pregnant or breastfeeding women. Written informed consent was obtained from patients for the anonymous use of the data.

**Medication**

PR OXN is available in 5mg/2,5mg; 10mg/5mg; 20mg/10mg and 40mg/20mg (oxycodone/naloxone) tablets and was prescribed to the patients according to the SPC.Patients were switched immediately from PR OXY to PR OXN with equal oxycodone doses. After switch to PR OXN the PR OXN dose could be titrated as needed, Use of laxatives and analgesic rescue medication as well as other co-medication was allowed during PR OXN treatment as in daily clinical practice and documented (yes/no was mandatory, type and dosage was optional).

**Study assessments**

*Primary parameter*

The primary parameter was the percentage of responders after 12 weeks of PR OXN treatment. The response was based on the parameters pain and OIC as described below.

*Pain*

Pain was assessed at each visit by the physician on a numerical rating scale (NRS) from 0 (no pain) to 10 (worst pain).

*OIC*

OIC was evaluated by the physician using the validated BFI*[17,18]. This index uses a numerical scale from 0 (easy/no difficulty) to 100 (severe difficulty/very strong) to record a patients' subjective assessment of three items related to OIC: ease of defecation, feeling of incomplete bowel evacuation and personal judgement of OIC. The BFI is calculated as the arithmetic mean of the scores for these three items. A lower score indicates a better bowel function. A score of ≤28.8 is considered a normal bowel function with respect to OIC and a BFI change of ≥12 points is considered a clinically relevant change[17,18,19].

* 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.

*Responders*

A patient was defined as a responder if the patient had:

- no worsening of pain (NRS increase ≤ 1 unit at visit 3/last visit compared to visit 1 or a NRS ≤ 4 at visit3 /last visit AND
- had a reduction in BFI of ≥ 12 units at the last visit compared to visit 1 or a BFI ≤ 28.8 at visit 3/last visit.

*Secondary parameters*

Secondary parameters included the use of laxatives and analgesic rescue medication, evaluation of the quality of life and safety assessment during PR OXN treatment compared to the previous PR OXY treatment.

*Use of laxatives*

Laxative use was assessed by asking if the patient had used laxatives in the last 7 days prior to the each study visit (yes or no) and whether laxative use had increased/decreased or remained constant compared to previous visit was also registered (decrease/constant/increase). If laxatives were used in the last seven days prior to the study visit, notation of type, dose and frequency of the used laxatives were optional due to the non-interventional character of the study. The percentage of patients using laxatives in the last 7 days before each visit and the percentages of patients reporting increased/decreased/stable laxative use at visits 2 and 3 compared to visit 1 were calculated.

*Use of analgesic rescue medication*

The assessment of the use of analgesic rescue medication was similar to the assessment of laxative use as described above.

*Quality of Life*

The patient's quality of life was evaluated via the standardized EQ-5D questionnaire. The EQ-5D score and EQ-5D VAS health score was recorded at visit 1 and at the last visit. A derived EQ-5D score was calculated from the 5 items (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) as well as the absolute change in EQ-5D score and EQ-5D VAS health score between the last visit and visit 1.

*Safety*

Safety assessments consisted of monitoring and recording all (Serious) Adverse Events ((S)AEs) and adverse reactions (ARs) at all visits.

### Statistical analysis

For the efficacy parameters the analyses were performed for all patients meeting the inclusion criteria who received at least one dose of PR OXN treatment and who had at least one post-dose efficacy evaluation (full analysis population). Patients using laxatives during the 30 days PR OXY treatment were included in this full analysis. Since patients were not asked pro-actively about the laxative treatment before start, and since the laxative use during last 7 days was evaluated at the consecutive visits, it was decided to analyze the primary parameter also for patients who used laxatives in the last 7 instead of 30 days before study inclusion (per protocol population). The safety analysis was performed for all patients who had received at least one dose of study medication and had at least one safety assessment after the last dose (safety population). Descriptive statistics of all demographic, baseline variables and study parameters were provided overall. Continuous data were summarized by their mean, standard deviation, 95% confidence interval of the mean, median, minimum and maximum. Categorical and ordinal data were summarized by frequency and percentages. No imputation of missing data was performed. A paired t-test was used to test if there was a change in mean pain NRS, BFI and EQ- 5D score between the first and last visit. The McNemar test for paired data was used to test if there was a change in use of laxatives or use of analgesic rescue medication between the first and the last visit. The effect of the treatment time on changes in mean BFI scores was studied in more detail using linear mixed effect models. All statistical tests were performed using a two-sided significance level of 5%.

## RESULTS

A total of 68 patients were included in the full analysis population (Figure 1). 91.2% of the patients (62 out of 68) completed the study. Three patients (4.4%) discontinued the study on their own choice, one patient stopped due to an adverse event and 2 patients (2.9%) for other reasons ( Figure 1). For 3 subjects no laxative intake for the last 7 days was documented and therefore 65 patients were included in the per protocol analysis (Figure 1).

Table 1 shows age, gender and diagnosis of pain for enrolled patients. The median study duration was 91 days (7 - 127 days), with 37.5 days (3-85) for visit 2 (dose titration) and 91 day for visit 3 (39-127). These variations in study durations were due to the non-interventional set-up of the study. The median (range) dose of PR OXY treatment used before start of the study (visit 1) was 20 (5-360) mg. The median (range) prescribed dose of PR OXN at visit 1 was similar to that of PR OXY, 20 (10-360) mg. At visit 2 and visit 3 the median (range) dose of PR OXN remained stable at 20 (10-360) mg.

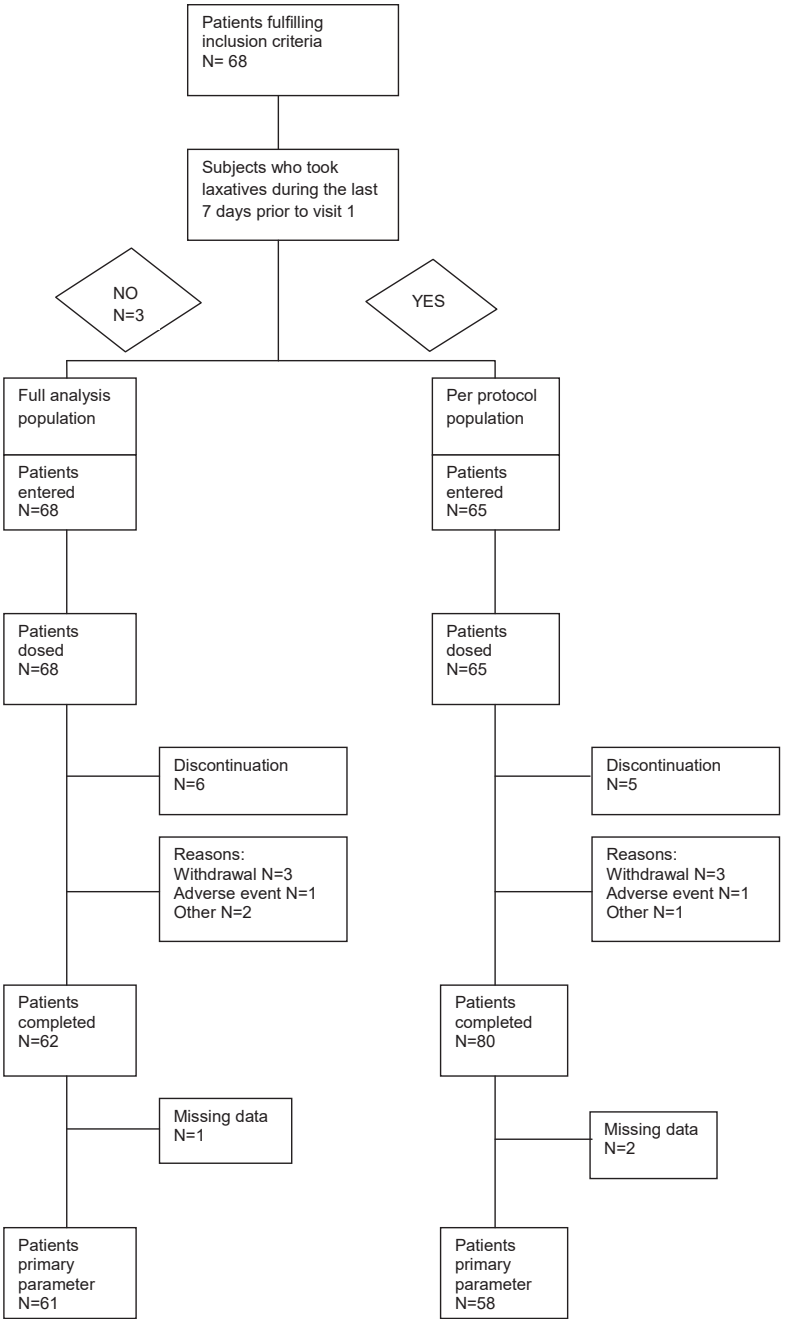


**Figure 1:** Patient diagram

The full analysis population included all patients meeting the inclusion criteria who received at least one dose of PR OXN treatment during the study and who had at least one post-dose efficacy evaluation. The per protocol population included all patients meeting the inclusion criteria who took laxatives in the last 7 days before study inclusion.

**Table 1:** Baseline characteristics of the patients (n=68, full analysis population)

| Characteristic | Value |
|---|---|
| Age (years), Mean (SD) | 59.8 (13.3) |
| Sex, no. (%) | |
| Male | 22 (32.4) |
| Female | 46 (67.6) |
| Pain diagnosis, no. (%) | |
| Malignant | 4 (5.9) |
| Non-malignant* | 62 (91.2) |
| Osteoarthritis | 19 (30.6) |
| Arthritis | 1 (1.6) |
| Low back pain | 26 (41.9) |
| Neuropathic pain | 22 (35.5) |
| Osteoporosis | 2 (3.2) |
| Post-operative pain | 6 (9.7) |
| Other | 9 (14.5) |
| Unknown | 2 (2.9) |

*For patients with non-malignant pain, multiple diagnoses were possible

### Efficacy of PR OXN treatment with regard to pain relief

The pain NRS reduced significantly ($p<0.001$) with on average 2.1 units (95% CI: 1.66, 2.54) between visit 1 (mean(SD) 6.8±1.5) and visit 3 (mean(SD) 4.6±1.5) (Figure 2). The average pain NRS was also significantly decreased over time during PR OXN treatment to 3.8 after 18 weeks.

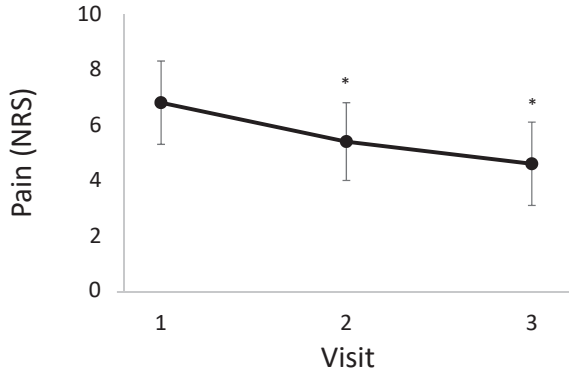


**Figure 2:** Average pain score (NRS) with standard deviation per visit (FA population).
Number of patients at visit 1 n=60, visit 2 n=59 and visit 3 n=54. * Indicate a significant reduction in pain NRS in comparison with visit 1 ($p<0.001$, linear mixed effect model).

### Efficacy of PR OXN treatment with regard to OIC

The BFI reduced significantly (p<0.001) with on average 48.5 units (95% CI: 44.4, 52.7) between visit 1 (mean(SD) 70.8±16.2) and visit 3 (mean(SD) 21.3±13.2) (Figure 3).

The BFI improved significantly (p<0.001) with on average 3.4 units (95% CI: -3.8, -3.0) per week during PR OXN treatment. This improvement of BFI was clinically relevant with an average of 13.6 units (95% CI: 12, 15.2) after already 4 weeks of PR OXN treatment. After 6 weeks of PR OXN treatment, the average BFI was <28.8 and thus patients were considered not constipated anymore.

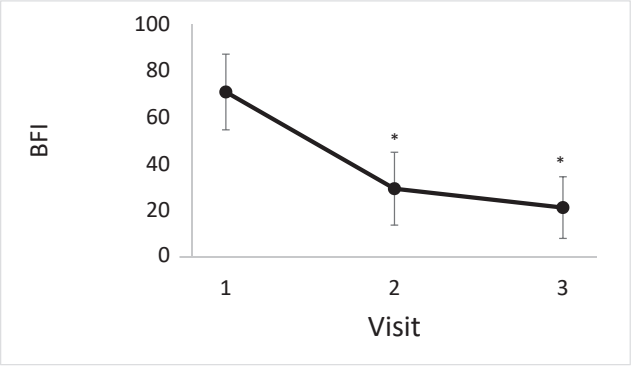


**Figure 3:** Average bowel function index (BFI) with standard deviations per visit (FA population). Number of patients at visit 1 n=67, visit 2 n=66 and visit 3 n=61. * Indicate a significant reduction in BFI in comparison with visit 1 p,.001, linear mixed effect model).

### Efficacy of PR OXN treatment in terms of responders

The efficacy of PR OXN regarding pain relief and OIC was expressed as the percentage of responders following 12 weeks PR OXN treatment compared to the previous PR OXY treatment. Data for 1 and 2 patients were missing for the full analysis and per protocol populations respectively (Figure 1, primary parameter). Among the full analysis population, 58 out of 61 patients were qualified as responders (95.1%, 95% CI: 86.0%; 98.9%) and for the per protocol population 55 out of 58 patients (94.8%, 95% CI: 85.3%; 98.8%) were qualified as responders.

### Use of laxatives

The number of patients using laxatives in the last 7 days before each visit decreased significantly from 65 patients (95.6%) at start to 24 patients (38.7%) at visit 3 (McNemar test $\chi^2(1) = 37.0$, p<0.001)(Table 2).

The optional field for type of laxative was registered for 32 out of 65 patients at visit 1; the majority of these patients (73%) used polyethylene glycol (PEG), 30% bisacodyl,

**Table 2:** Laxative use in the 7 days before the study visit. Data are given as no. (%).

| Laxative use | Visit 1 [A] *n* (%) | Visit 2 [B] *n* (%) | Visit 3 [B] *n* (%) | Last visit [B] *n* (%) |
|---|---|---|---|---|
| Yes / No | 65 / 3 (95.6 / 4.4) | 41 / 26 (60.3 / 38.2) | 24 / 38 (38.7 / 61.3) | 26 / 42 (38.2 / 61.8) |
| Decrease / Constant / Increased [C] | NA | 37 / 3 / 1 (90.2 / 7.3 / 2.4) | 20 / 4 / 0 (83.3 / 16.7 / 0) | 21 / 5 / 0 (80.8 / 19.2 / 0) |
| Missing data | 0 | 1 (1.5) | 0 | 0 |

NA = not available

[A] Laxative used in last 7 days before study inclusion. These data are considered data for laxative use during the previous PR OXY treatment.

[B] Laxative used in last 7 days before study visit: yes/no and increased, decreased or constant laxative use during PR OXN treatment compared to the preceding PR OXY treatment.

[C] Decrease / Constant / Increased laxative use for patients who used laxatives during the preceding PR OXY treatment

17% sodium picosulphate, 17% senna, 8% lactulose and 8% rectal laxatives. Since more than one laxative could be registered the sum of these percentages is >100%.

Within the group of 41 patients using laxatives at visit 2, 37 patients (90.2%) reported a decreased use of laxatives in the last 7 days compared to the preceding PR OXY treatment. Of the 24 patients using laxatives at visit 3, 20 patients (83.3%) reported a decreased use of laxatives in the last 7 days compared to the preceding PR OXY treatment.

### Use of analgesic rescue medication

The number of patients using analgesic rescue medication in the last 7 days before each study visit decreased significantly from 44 patients (64.7%) at start to 26 patients (41.9%) at visit 3 (McNemar test $\chi^2(1) = 13.1$, $p<0.001$). The optional field for type of rescue medication was registered for 28 out of 44, 19 out of 37 and 15 out of 26 patients at visit 1,2 and 3 respectively. The majority of these patients (V1 68%, V2 63% and V3 66%) used oxycodone as rescue medication.

### Quality of life

The EQ-5D score increased significantly with on average 0.275 units (95% CI: 0.202; 0.347) between visit 1 (mean(SD) 0.247±0.233) and the last visit (mean 0.522±0.275) ($p<0.001$) . The EQ-5D VAS health score increased significantly with on average 25.2 units (95% CI: 20.1; 30.3) between visit 1 (mean(SD) 33.0±13.0) and the last visit (mean 58.2±16.8) ($p<0.001$).

### Safety analysis

Only two patients (2.9%) reported an adverse event. One patient reported euphoria and drowsiness at visit 2. The other patient had an epileptic seizure after visit 2, however, this

was considered to be unrelated to PR OXN treatment. AEs were of average intensity and were pharmacologically treated, leading to disappearance of the AE. No serious adverse event (SAE) was reported throughout the study.

## DISCUSSION

This study, requested by the Belgian reimbursement authorities evaluated the efficacy of PR OXN regarding pain relief and OIC in 68 patients with chronic pain who were treated with PR OXY during at least the last 30 days before PR OXN treatment and who suffered from OIC despite the use of at least 2 laxatives with different mechanisms of action (level 4 ATC term). To the best of our knowledge, this is the only non-interventional study of opioid treatment where laxative use is documented before and during opioid treatment.

This study shows that PR OXN was superior to PR OXY regarding pain relief, OIC and quality of life in chronic pain patients previously treated with PR OXY and suffering from OIC despite the use of at least 2 different laxatives. The mean pain NRS reduced significantly with on average 2.1 units during treatment with PR OXN, comparable to other studies previously demonstrating similar analgesic efficacy of PR OXN and PR OXY even after long-term treatment with PR OXN[4, 9, 12-15]. The median PR OXN daily dose of 20 mg remained constant throughout the study and was equal to the PR OXY dose during the preceding PR OXY treatment. Moreover, the use of analgesic rescue medication decreased significantly during PR OXN treatment compared to the preceding PR OXY treatment. The observed improved pain relief during PR OXN treatment can therefore not be explained by an increased dose or increased use of analgesic rescue medication and is probably related to the improved OIC during PR OXN treatment.

This is the first non-interventional study in which the effect of PR OXN on OIC was evaluated using two parameters, i.e. the BFI and laxative use. The BFI showed a statistically significant and clinically relevant improvement of 49 points from visit 1 to the last visit. A change in BFI of ≥ 12 points is proven to be related to clinically meaningful changes of bowel habits in patients with OIC[18].This study confirms that after 4 weeks of treatment with PR OXN a clinically relevant improvement of OIC is attained in patients suffering from laxative-refractory OIC. The average BFI was below 28.8 after 6 weeks of PR OXN treatment, indicating that patients were on average not constipated anymore despite the opioid treatment[19].

In addition to the BFI, PR OXN efficacy regarding OIC was investigated by comparing the use of laxatives between the previous PR OXY treatment and PR OXN treatment. The number of patients using laxatives declined significantly during PR OXN treatment compared to PR OXY. If laxatives were needed, the vast majority of patients using laxatives during PR OXN treatment indicated decreased laxative use during PR OXY treat-

ment. Therefore, the improvement in OIC observed during PR OXN treatment cannot be explained by an increased use of laxatives. This supports the rationale that PR OXN treatment counteracts OIC through other mechanisms than laxatives do and that PR OXN addresses the underlying mechanism of OIC. The results of this non-interventional study are in line with results of a pooled analysis of laxative-refractory OIC patients from studies with PR OXN with respect to BFI and laxative use[20]. This pooled analysis showed that PR OXN significantly improved bowel function and reduced the use of laxatives in patients with OIC, previously unresponsive to at least two different classes of laxatives.

PR OXN also provided effective analgesia for patients with moderated-to-severe cancer-related pain and non-cancer-related pain. The efficacy of PR OXN regarding pain relief and OIC was expressed as the percentage responders following PR OXN treatment compared to the previous analgesic treatment with PR OXY. The percentage of responders was 95.1% after 12 weeks of PR OXN treatment, indicating that almost all patients experienced a pain NRS score ≤ 4 or improved pain relief in the absence of OIC (BFI ≤ 28.8) or with a clinical improvement in OIC (BFI improvement ≥ 12 units) compared to the preceding PR OXY treatment.

Quality of life improved significantly during PR OXN treatment. The overall EQ-5D score and EQ-5D VAS health score increased significantly with on average 0.275 units and 25.2 units resp. after 12 weeks of PR OXN treatment compared to PR OXY. This improved quality of life probably reflects the improved pain relief and OIC during PR OXN treatment and is in line with previous studies[4, 16, 21].

PR OXN treatment was well tolerated in this study. No SAEs were reported during this study. The frequency of AEs was lower compared to other studies, which can be explained by the observational design of this study.

Remarkably, in this study one patient was directly switched from a daily dose of 360 mg oxycodone to an equivalent dose of 360 mg/180 mg oxycodone/naloxone. In current literature daily doses of up to 240 mg/120 mg oxycodone/naloxone have been described using a stepwise switch from oxycodone to oxycodone/naloxone with different outcomes[14,22]. Close review of the patient's records revealed that the patient responded well to the direct switch. Pain relief on oxycodone was comparable to pain relief on oxycodone/naloxone (pain NRS score was 3 throughout the 87 days treatment period). Moreover, no adverse events were reported, the patient did not require any analgesic rescue medication or other concomitant medication and a decrease in laxative medication was reported alongside an improvement in bowel function after switch from oxycodone to oxycodone/naloxone (BFI decreased from 46.7 to 0).

Of course a non-interventional study has limitations, one of them being that we could not ensure that all data were documented in the database. This limitation was tackled by marking important parameters (e.g. BFI, pain relief, laxative use yes/no and rescue

medication yes/no) as mandatory fields in the electronic CRF, as a result there were hardly any missing data for these mandatory fields.

Whilst keeping the inherent limitations of a non-interventional study in mind the effects of PR OXN in real-life clinical practice in Belgium for those patients who were eligible for reimbursement, demonstrated significant reduction of OIC during treatment of PR OXN in laxative-refractory OIC patients. The results of this real-life study confirmed the improvement seen in a pooled analysis from pivotal studies with PR OXN in a comparable patient group[20].

## CONCLUSION

In this real-life study in Belgium, patients with chronic severe pain and OIC despite the use of at least 2 laxatives with different mechanisms of action (level 4 ATC term) experienced a significant improved pain relief, a significant and clinically relevant reduction of OIC as well as a significant improvement of quality of life after PR OXN treatment compared to previous PR OXY treatment. The percentage of responders was 95.1% after 12 weeks of PR OXN treatment, indicating that almost all patients experienced no pain or improved pain relief in the absence of OIC or with a clinical improvement in OIC compared to the preceding PR OXY treatment.

## TRANSPARENCY

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