Effectiveness of naloxegol in patients with cancer pain and opioid-induced constipation – The MovE study

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RESPONSIBLE USAGE

MOVENTIG (naloxegol) is indicated for the treatment of opioid-induced constipation (OIC) in adult patients who have had an inadequate response to laxative(s). For advice on the responsible use of opioids to treat pain, please click here

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MovE: study introduction[1] (1/2)

- Opioids are recommended to control **moderate-to-severe cancer pain**[1]
- Opioid-induced constipation (OIC) is the **most common side effect** of these drugs and is the result of the binding of opioids to the μ-receptor in the gastrointestinal tract[2,3]
- Patients with OIC report significantly worse **quality of life** compared with non-constipated patients and it has been reported that **about a third of patients** reduced or stopped taking opioids because of OIC[4]
- **Laxatives** are a common first-line therapeutic strategy for OIC, however up to **81%** of chronic pain patients on opioids are estimated to be struggling with **OIC, despite using laxatives**[4,5]

OIC, opioid-induced constipation.

1. World Health Organization (2019). WHO guidelines for the pharmacological management of cancer pain in adolescents and adults. https://apps.who.int/iris/bitstream/handle/10665/279700/9789241550390-eng.pdf?ua=1 Accessed June 2023; 2. Lacy, BE, *et al. Gastroenterology* 2016;150:1393; 3. Tuteja AK, *et al. Neurogastroenterol Motil* 2010;22(4):424–30; 4. Bell TJ, *et al. Pain Med* 2009;10(1):35–42; 5. Farmer, AD *et al. UEG Journal* 2019;7(1):7–20.

MovE: study introduction[1] (2/2)

- Peripherally-acting mu-opioid receptor antagonists (**PAMORAs**) function in the gastrointestinal tract, decreasing the constipating effects of opioids without impacting opioid-mediated analgesic effects on the central nervous system[1]
- **Naloxegol** is a PEGylated derivative of the mu-opioid receptor antagonist naloxone and is an oral once-daily PAMORA[1]
  - The recommended dose of naloxegol is 25 mg daily, although a starting dose of 12.5 mg daily is recommended for patients with moderate or severe renal insufficiency or taking moderate CYP3A4 inhibitors. The dose can be increased to 25 mg in these patients if 12.5 mg is well tolerated[1]
- **Clinical efficacy and safety** of naloxegol have been demonstrated in **non-cancer patients** in two 12-week Phase III studies[2–4]
  - An open-label, randomised, parallel-group phase III study in **non-cancer patients** over 52 weeks showed the **long-term tolerance** of naloxegol 25 mg[4]
- Two recent real-world studies (**KYONAL, NACASY**) investigated the **efficacy and safety of naloxegol in cancer patients with OIC** respectively up to 1 year and during a 4-week follow-up period[5,6]
- The **MovE study** was designed to assess the efficacy and safety of naloxegol therapy in **real-life conditions** in cancer pain patients as well as changes to quality of life, constipation and other symptoms related to OIC[2]

OIC, opioid-induced constipation.

1. **MOVENTIG** Summary of Product Characteristics; 2. Lemaire, A, *et al. Supp Care Cancer* 2021;29:7577; 3. Chey, WD, *et al. N Engl J Med* 2014;370:2387; 4. Webster, L, *et al. Aliment Pharmacol Ther* 2014;40(7):771; 5. Cobo, Dols M, *et al. BMJ Support Palliat Care* 2021 Mar 11; bmjspcare-2020-002816; 6. Davies, A, *et al. Cancers* 2022;14:1128. doi: 10.3390/cancers14051128

MovE[1]

Supportive Care in Cancer (2021) 29:7577–7586
https://doi.org/10.1007/s00520-021-06299-2

ORIGINAL ARTICLE

Check for updates

Effectiveness of naloxegol in patients with cancer pain suffering from opioid-induced constipation

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Abstract

Purpose Naloxegol, an oral once-daily peripherally acting mu-opioid receptor antagonist, is indicated for the treatment of opioid-induced constipation (OIC) with inadequate response to laxative(s), in cancer and non-cancer patients. This study mainly aimed to assess in real-life conditions the efficacy and safety of naloxegol in cancer pain patients and the evolution of their quality of life.

Methods A non-interventional, 4-week follow-up study was conducted in 24 French oncology and pain centers between 2018 and 2019. Eligible patients were aged ≥ 18 years, treated with opioids for cancer pain, and started naloxegol for OIC with inadequate response to laxatives. The rate of the response to naloxegol (primary criterion) was assessed at W4. The evolution of quality of life was measured using the Patient Assessment of Constipation Quality of Life (PAC-QOL).

Results A total of 124 patients were included (mean age, 62 ± 12 years; ECOG ≤ 2, 79%; primary cancer, lung 18%, breast 16%, prostate 11%, head and neck 9%, digestive 9%…; metastatic stage, 80%). At inclusion, the median opioid dosage was 60 mg of oral morphine or equivalent. At W4, the response rate was 73.4% (95% CI [63.7–83.2%]), and 62.9% (95% CI [51.5–74.2%]) of patients had a clinically relevant change in quality of life (decrease in PAC-QOL score ≥ 0.5 point). Adverse events related to naloxegol were reported in 8% of patients (7% with gastrointestinal events; one serious diarrhea).

Conclusion This real-world study shows that naloxegol is effective and well tolerated in cancer pain patients with OIC and that their quality of life improves under treatment.

Keywords Cancer · Constipation · Naloxegol · Opioids · Pain

1. Lemaire, A, *et al. Supp Care Cancer* 2021;29:7577.

MovE: study summary[1]

- Four-week, non-interventional, prospective real-world study in adult patients with cancer and OIC in 24 centres in France (pain units, oncology units, palliative care units)

- **Primary efficacy endpoint**: Response rate during the 4 weeks of treatment (proportion of patients reporting ≥3 bowel movements in Week 4, with or without combined laxatives during follow-up, and an increase of ≥1 bowel movement per week between inclusion and Week 4)
  - **Efficacy Population (N=124)** patients who fulfilled all selection criteria. 86 completed the study to Week 4 and 79 were evaluable for the primary efficacy endpoint

- **Safety analyses**: adverse events, seriousness and causal relationship with naloxegol
  - **Safety population (N=131)** patients who received at least one dose of naloxegol

- **133** patients were **included** and treated in **routine clinical practice** according to the naloxegol SmPC

OIC, opioid induced constipation; SmPC, summary of product characteristics

1. Lemaire, A, *et al. Supp Care Cancer* 2021;29:7577.

MovE: other endpoints and analyses[1]

- **Subgroup analysis:** The primary endpoint (response rate at 4 weeks) was analysed separately to assess any differences between patients with or without concomitant laxative use at follow-up

Other endpoints recorded:

- Bowel Function Index (BFI)
- Patient Assessment of Constipation Symptoms (PAC-SYM)
- Patient Assessment of Constipation Quality of Life (PAC-QOL)
- Physician- and patient-reported satisfaction with naloxegol

1. Lemaire, A, *et al. Supp Care Cancer* 2021;29:7577.

MovE: questionnaires used in the study[1]

- **BFI**: a physician-administered questionnaire consisting of 3-item patient-assessment scale (ease of defaecation, feeling of incomplete bowel evacuation, and personal judgement of constipation
  - **Scored** on numerical 0–100 scales; a 12-point change in score constitutes a clinically relevant change in constipation
- **PAC-SYM**: 12-item self-reported questionnaire to assess symptoms of constipation, divided into 3 symptoms subscales – abdominal, rectal and stool
- **PAC-QOL**: 28-item self-reported questionnaire designed to evaluate the burden of constipation on patients' everyday HRQoL, covering the specific constipation-related domains of worries and concerns, physical discomfort, psychosocial discomfort and satisfaction
  - **PAC-SYM** and **PAC-QOL** are scored on a 5-point Likert scale (0 – not at all, to 4 – extremely) and for both, a ≥0.5 point-change corresponds to a minimal important difference

BFI, Bowel Function Index; HRQoL, health-related quality of life; PAC-QOL, Patient Assessment of Constipation Quality of Life Questionnaire; PAC-SYM, Patient Assessment of Constipation Symptoms

1. Lemaire, A, *et al. Supp Care Cancer* 2021;29:7577.

MovE: inclusion criteria†

- Patients ≥18 years old with cancer pain[1]
- Treated with step II or III opioids[2]* for their cancer pain
- Starting naloxegol treatment for OIC after an inadequate response to laxative(s), i.e. persistence of OIC symptoms despite the use of laxatives ≥4 days prior to inclusion[1]
- Able to complete self-reported questionnaires and with no objection to participate in the study[1]
- OIC was defined in accordance with the ROME IV criteria for OIC[1]**

†Patients participating in an interventional study or with evidence of digestive obstruction were excluded.[1]

*Step II: weak opioid (e.g. codeine) + non-opioid, ± adjuvant; step III: strong opioid (e.g. morphine) ± non-opioid, ± adjuvant[2]

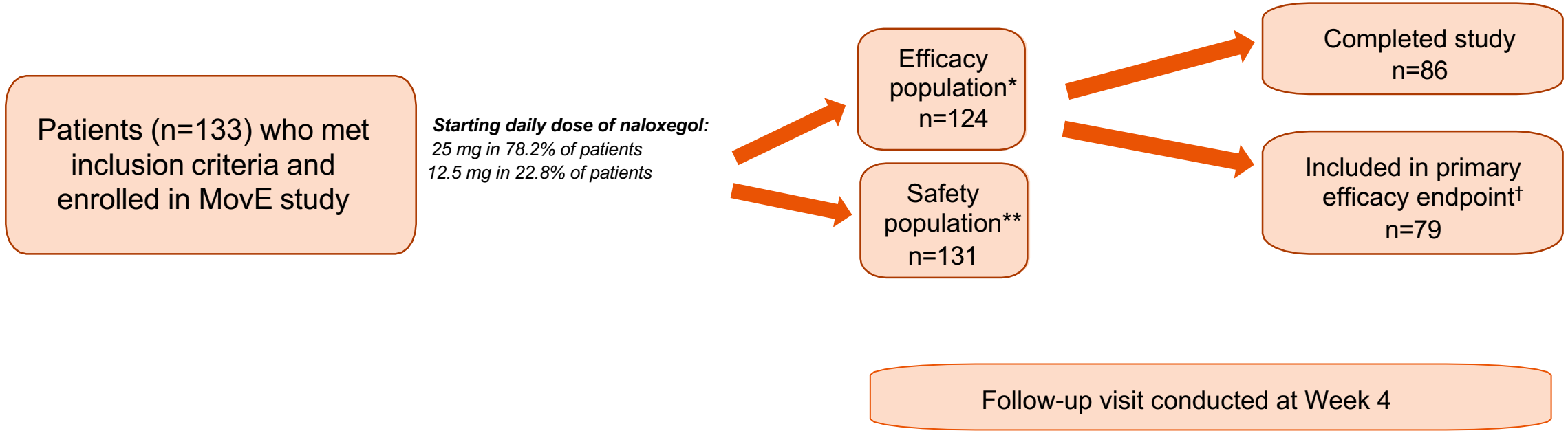
**1) New, or worsening, symptoms of constipation when initiating, changing, or increasing opioid therapy, that must include two or more of the following: a. Straining during more than ¼ (25%) of defecations b. Lumpy or hard stools (Bristol Stool Form Scale 1-2) more than ¼ (25%) of defecations c. Sensation of incomplete evacuation more than ¼ (25%) of defecations d. Sensation of anorectal obstruction/blockage more than ¼ (25%) of defecations e. Manual maneuvers to facilitate more than ¼ (25%) of defecations (e.g. digital evacuation, support of the pelvic floor) f. Fewer than three SBM per week; 2) Loose stools are rarely present without the use of laxatives.[3]

OIC, opioid induced constipation; SBM, spontaneous bowel movement

1. Lemaire, A, *et al. Supp Care Cancer* 2021;29:7577; 2. World Health Organization (1986). Cancer pain relief. Accessed June 2023; 3. Lacy, BE, *et al. Gastroenterology* 2016;150:1393.

MovE: study design[1]

- MovE was a 4-week, single-arm, open-label, prospective real-world observational study



*Patients who had met all selection criteria, had received at least one dose of naloxegol, and had least one post-baseline efficacy assessment;
**Patients who met all selection criteria and had received at least 1 dose of naloxegol;

†Response rate during the 4 weeks of treatment (proportion of patients reporting ≥3 bowel movements in Week 4, with or without combined laxatives during follow-up, and an increase of ≥1 bowel movement per week between inclusion and Week 4)

1. Lemaire, A, *et al. Supp Care Cancer* 2021;29:7577.

MovE: selected baseline characteristics[1] (1/2)

Most frequent **primary tumour** locations: **lung 17.7%** (n=22), and **breast 16.1%** (n=20); of those with solid tumours, **80.0%** (n=80) had **metastases**

54.0% of patients (n=67) were **receiving chemotherapy** treatment at study entry

Most commonly used **opioids at inclusion: oxycodone** (54.8%), **morphine** (33.9%), **fentanyl** (29.0%), **tramadol** (7.3%)

Median duration of treatment with **laxatives** was **32.5 days** (IQR, 11.0 – 112.0).
Most commonly used laxatives were **osmotics** (93.5%)

1. Lemaire, A, *et al. Supp Care Cancer* 2021;29:7577.

MovE: selected baseline characteristics[1] (2/2)

Baseline parameters	Analysed patients (N)	Efficacy population (N=124)
Age (years), mean (SD)	124	62.1 (12.1)
Age <70 years, n (%)	124	95 (76.6)
Male sex, n (%)	124	117 (63.2)
Body mass index (kg/m^2), mean (SD)	114	23.8 (4.7)
ECOG index, n (%)	121	
≤2		95 (78.5)
>2		26 (21.5
Concomitant diseases, n (%)	124	34 (27.4)
Chronic kidney disease		8 (6.5)
Diabetes		6 (4.8)
Hypertension		5 (4.0)
Duration of OIC (weeks), median (IQR)	124	4.9 (1.6–10.9)
BFI total score, mean (SD)	118	71.2 (19.6)
PAC-SYM total score, mean (SD)	107	2.2 (1.2)
PAC-QOL total score, mean (SD)	104	2.1 (0.6)

BFI, Bowel Function Index; ECOG, Eastern Cooperative Oncology Group (ECOG); IQR, interquartile range; PAC-SYM, Patient Assessment of Constipation Symptoms; PAC-QOL, Patient Assessment of Constipation Quality of Life; SD, standard deviation.

1. Lemaire, A, *et al. Supp Care Cancer* 2021;29:7577.

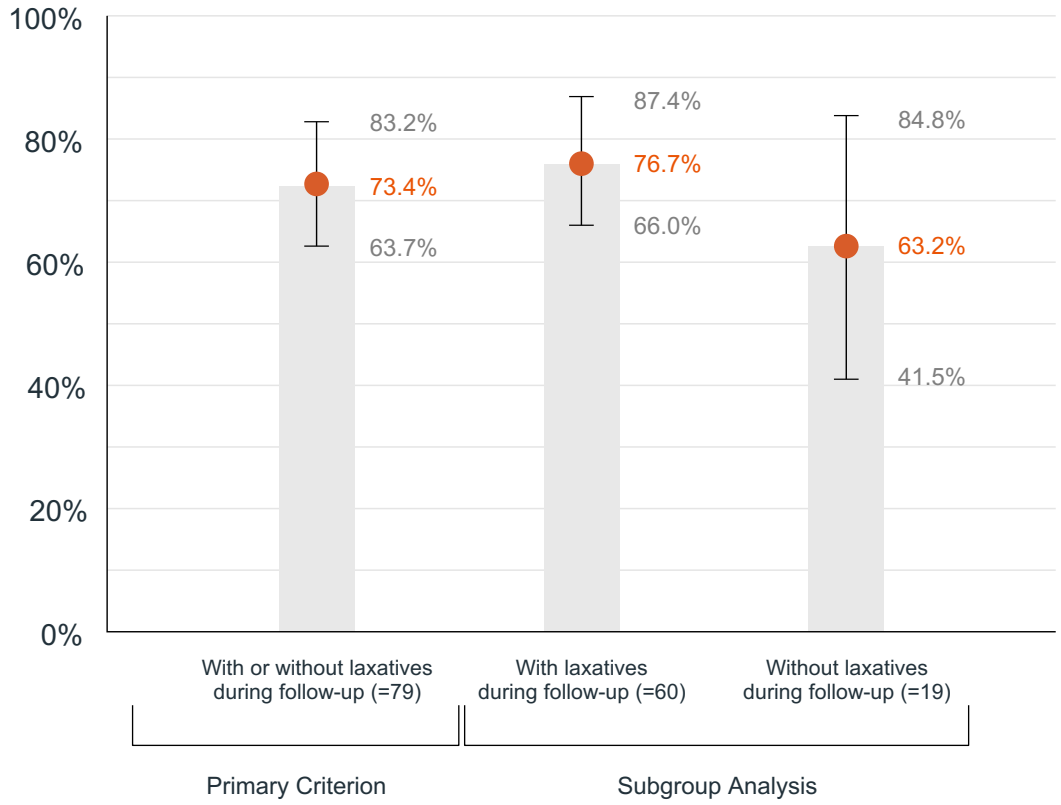
MovE: baseline treatment[1]

% patients taking medication*		
Opioids administered for the treatment of pain	Oxycodone Morphine Fentanyl Tramadol Opium Codeine Methadone	54.8 33.9 29.0 7.3 2.4 1.6 0.8
Other treatments that could lead to constipation	Grade 1 analgesic Anxiolytic Antidepressant Steroid Anticonvulsant Antispasmodic Anticholinergic	74.4 33.1 27.3 22.3 18.2 9.1 5.8
Previous laxative treatments for OIC	Osmotic Enema Bulking agents	93.5 9.7 5.6

*More than one medication in each class may be prescribed
OIC, opioid induced constipation

1. Lemaire, A, *et al. Supp Care Cancer* 2021;29:7577.

Primary efficacy endpoint: Response rate to naloxegol at Week 4[1]



- Most of the 79 evaluable patients in the efficacy population responded to naloxegol treatment
  73.4%, 95% CI [63.7–83.2%]
- Response was irrespective of the use of laxatives during patient follow-up
  76.7% [66.0–87.4%] vs **63.2%** [41.5–84.8%]

CI, confidence interval

Response to naloxegol was defined as follows: ≥3 bowel movements during the 4th week after inclusion and an increase from baseline of ≥1 bowel movement per week between inclusion and the 4th week. The proportions of responder patients at the 4th week are graphically presented with their associated confidence intervals.

1. Lemaire, A, *et al. Supp Care Cancer* 2021;29:7577. Figure adapted from "Fig. 1 Response to naloxegol at week 4" by Lemaire, A, *et al. Supp Care Cancer* 2021;29:7577 Available at: https://pubmed.ncbi.nlm.nih.gov/34120247/

Effectiveness measures from patient diary data

- **62 patients** completed assessable diaries during the 4-week study period
- Based on diary data, the **response rate** (with or without laxatives during follow-up) was close to the estimate reported by physicians (**69.4%**, 95% CI [57.9–80.8%])
- Mean number (SD) of **bowel movements per week increased** from 2.1 (1.9) at baseline to 3.9 (2.1) at Week 4
- **68.7%** of patients had a stool the **first day or the day** after the first dose of naloxegol

CI, confidence interval; SD, standard deviation

1. Lemaire, A, *et al. Supp Care Cancer* 2021;29:7577.

Baseline predictors of response to naloxegol at Week 4[1]

Bone metastasis and taking opioids for <9 weeks at baseline were independent predictors of response to naloxegol at Week 4

Baseline parameters	Univariate OR [95% CI] (*p-value*)	Multivariate OR [95% CI] (*p-value*)
Metastatic stage of cancer	2.31 [0.67–8.01] *0.1861*	
Bone metastasis	**2.99 [0.97–9.23] *0.0574***	**3.62 [1.02–12.82] *0.0473***
Duration of opioids <9 weeks (median)	**5.14 [1.63–16.18] *0.0051***	**5.16 [1.59–16.77] *0.0063***
Duration of OIC <1.12 months (median)	3.14 [1.02–9.66] *0.0455*	
Mean number of stools over last 7 days	0.71 [0.50–1.01] *0.0584*	
Abdominal symptoms (mean PAC-SYM subscore)	0.59 [0.33–1.07] *0.0808*	
Concomitant analgesics	3.39 [1.16–9.90] *0.0259*	
Concomitant anxiolytics	3.78 [0.99–14.44] *0.0520*	
Concomitant antispasmodics	0.22 [0.03–1.44] *0.1143*	
Start dose of naloxegol 12.5 mg	0.38 [0.13–1.14] *0.0845*	

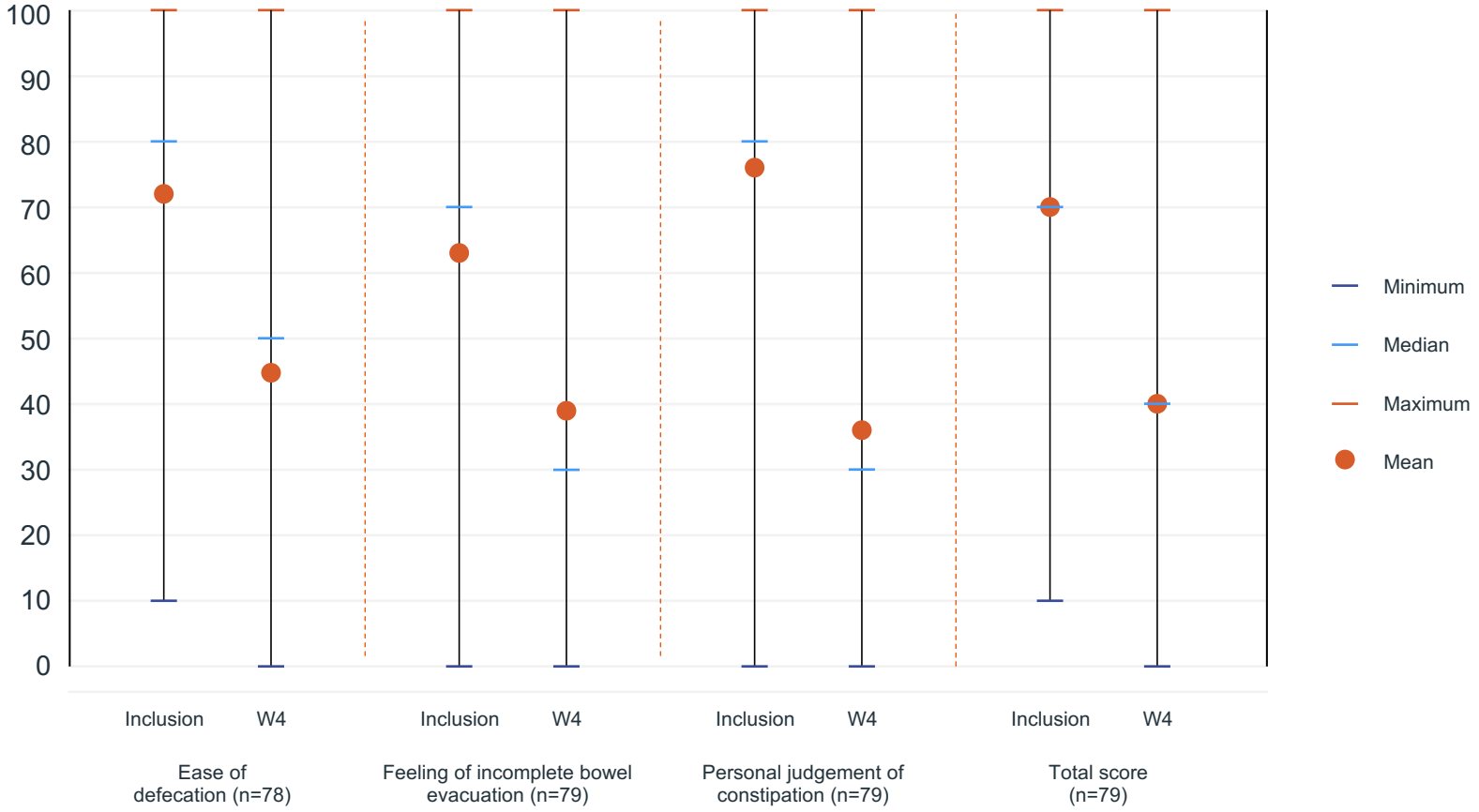
Logistic regression analysis. Factors significant at the 20% level are presented for univariate analysis and entered the final model; factors significant at the 5% are presented for multivariate analysis

CI, confidence interval; OIC, opioid induced constipation; OR, odds ratio.

1. Lemaire, A, *et al. Supp Care Cancer* 2021;29:7577.

Improvement in bowel function at Week 4

Total BFI* score (0–100) and its subscales



- **BFI** mean total score **improved** from baseline to 4 weeks of follow-up; from **70.9** SD (19.2) to **40.0** SD (26.0)
- The strongest improvement was in the '**personal judgement of constipation**' subscale; from **77.0** SD (23.2) to **37.2** SD (28.8)

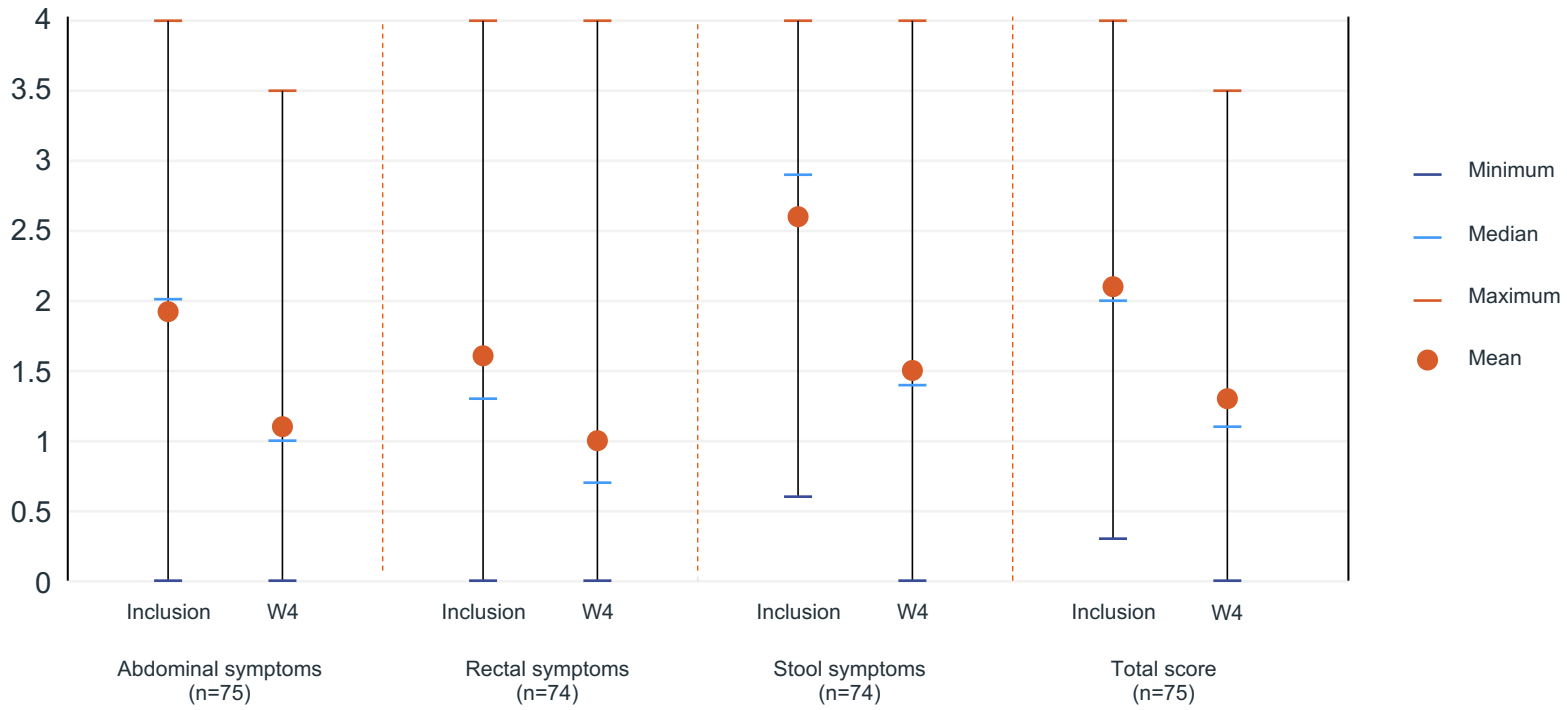
*Physician-administered questionnaire consisting of 3-item numerical 0–100 scales to assess symptoms of constipation

BFI, bowel function index; SD, standard deviation; W, week

1. Lemaire, A, *et al. Supp Care Cancer* 2021;29:7577 Figure adapted from "Fig 2.B Evolution of the constipation symptoms of patients" by Lemaire, A, *et al. Supp Care Cancer* 2021;29:7577 Available at: https://pubmed.ncbi.nlm.nih.gov/34120247/ Licensed under CC BY 4.0

Improvement in constipation symptoms at Week 4

Total PAC-SYM* score (0–4) and its subscales



- **PAC-SYM** mean total score **improved** from baseline to 4 weeks of follow-up; from **2.1** SD (0.7) to **1.3** SD (0.8)
- The strongest improvement was in the '**stool symptoms**' subscale; from 2.6 SD (0.8) to **1.5** SD (0.9)

*12-item self-reported questionnaire to assess symptoms of constipation, divided into 3 symptoms subscales where 0 – not at all, to 4 – extremely)

PAC-SYM, Patient Assessment of Constipation Symptoms; SD, standard deviation; W, week

1. Lemaire, A, *et al. Supp Care Cancer* 2021;29:7577 Figure adapted from "Fig. 2A Response to naloxegol at week 4" by Lemaire, A, *et al. Supp Care Cancer* 2021;29:7577 Available at: https://pubmed.ncbi.nlm.nih.gov/34120247/ Licensed under CC BY 4.0

Clinically important improvements in bowel function and symptoms of OIC at Week 4[1]

73.4% of patients (95% CI 63.7–83.2%) had **Bowel Function Index score change of ≥12 points** at end of study

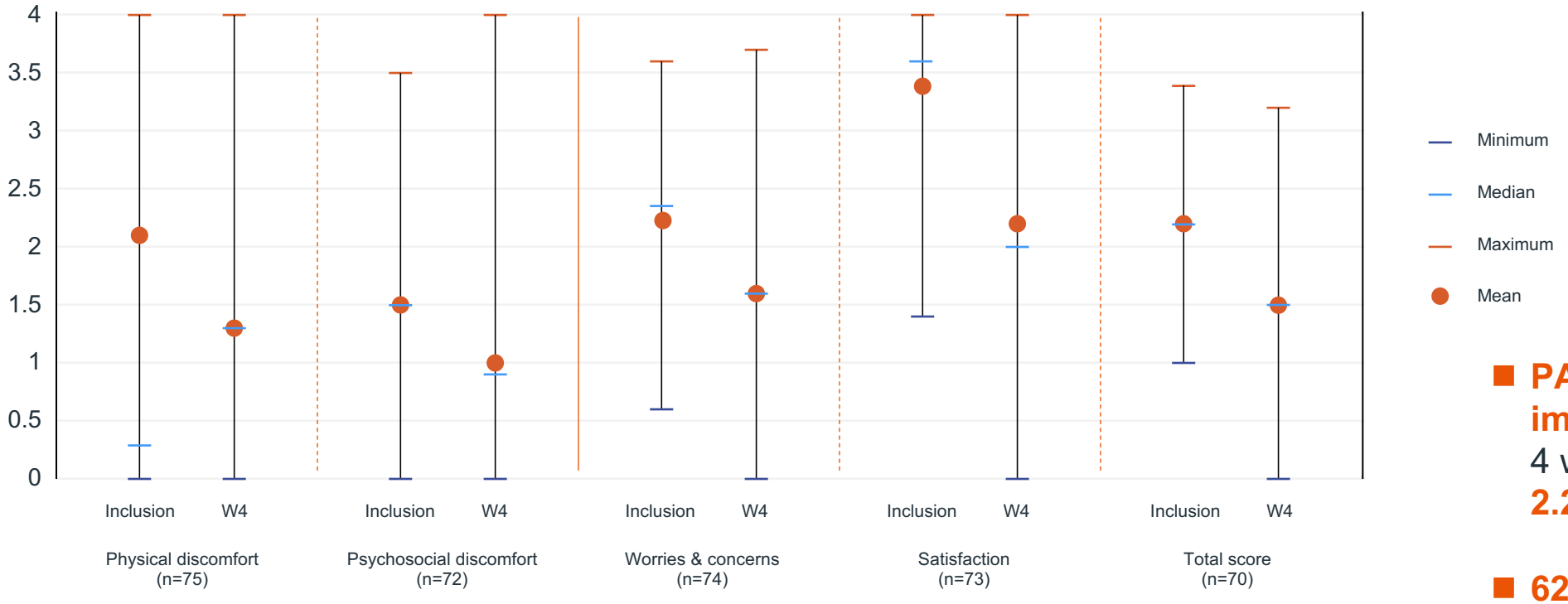
70.7% of patients (95% CI 60.4–81.0%) had **PAC-SYM score change of ≥0.5 points** at end of study

CI, confidence interval; OIC, opioid induced constipation; PAC-SYM, Patient Assessment of Constipation Symptoms.

1. Lemaire, A, *et al. Supp Care Cancer* 2021;29:7577

Improvement in quality of life at Week 4

Total mean PAC-QOL* score (0–4) and its subscales



- **PAC-QOL** mean total score **improved** from baseline to 4 weeks of follow-up; from **2.2** SD (0.6) to **1.5** SD (0.7)
- **62.9%** of patients had a **clinically relevant change**** in quality of life

*28-item self-reported questionnaire to evaluate the burden of constipation on patients' everyday HRQoL, scored on a 5-point Likert scale (0 – not at all, to 4 – extremely)
**a ≥0.5 point-change corresponds to a minimal important difference in quality of life

HRQoL, health-related quality of life; PAC-QOL, Patient Assessment of Constipation Quality of Life; SD, standard deviation; W, week

1. Lemaire, A, *et al. Supp Care Cancer* 2021;29:7577 Figure adapted from "Evolution of the quality of life of patients" by Lemaire, A, *et al. Supp Care Cancer* 2021;29:7577 Available at: https://pubmed.ncbi.nlm.nih.gov/34120247/ Licensed under CC BY 4.0

Physician and patient satisfaction with naloxegol[1]

After 4 weeks of treatment, the majority of physicians and patients reported satisfaction with naloxegol treatment

81.4% of **physicians**
and
72.4% of **patients**

gave a satisfaction rating of ≥5 out of 10

1. Lemaire, A, *et al. Supp Care Cancer* 2021;29:7577

MovE: adverse events[1]

- Overall, 43 of 131 patients (**32.8%**) reported **at least one adverse event**, and 21 (**16.0%**) at least one **serious adverse event**
- **15** adverse events considered to be **related to naloxegol** were reported in 11 patients (**8.4%**)
- **Treatment-related adverse events** were **mainly gastrointestinal**, with diarrhoea being the most frequently reported (n=9, 6.9%)
  - One **treatment-related SAE** was reported: diarrhoea (0.8% patients)
- 22 patients (**6.8%**) experienced **adverse events leading to discontinuation**, mainly cancer progression (6.1%) and diarrhoea (3.1%)
- **13 deaths** were associated with AEs, but none were considered to have a causal relationship with naloxegol

AE, adverse event; SAE, serious adverse event

1. Lemaire, A, *et al. Supp Care Cancer* 2021;29:7577

Adverse events related to naloxegol[1]

n (%)	Starting dose naloxegol 25 mg (n=102)	12.5 mg (n=29)	Total (N=131)
At least one related adverse event	9 (8.8)	2 (6.9)	11 (8.4)
Gastrointestinal disorders	7 (6.9)	2 (6.9)	9 (6.9)
Diarrhoea	5 (4.9)	-	5 (3.8)
Abdominal pain	1 (1.0)	1 (3.4)	2 (1.5)
Constipation	-	1 (3.4)	1 (0.8)
Nausea	1 (1.0)	-	1 (0.8)
Vomiting	1 (1.0)	-	1 (0.8)
Eructation	-	1 (3.4)	1 (0.8)
General disorders and administration	2 (2.0)	-	2 (1.5)
Pain	1 (1.0)	-	1 (0.8)
Withdrawal syndrome	1 (1.0)	-	1 (0.8)
Metabolism and nutrition disorders	1 (1.0)	-	1 (0.8)
Decreased appetite	1 (1.0)	-	1 (0.8)

1. Lemaire, A, *et al. Supp Care Cancer* 2021;29:7577

MovE: summary and conclusions

- The **MovE study** provides new information on the efficacy and safety of **naloxegol** for the treatment of OIC in cancer patients in a **real-world setting,** including in patients **continuing to use laxtives**[1]
- **Response rate of 73.4%** for naloxegol-treated patients at 4 weeks, irrespective of concomitant laxative use[1]
- **Efficacy and tolerability profiles** of naloxegol were **similar** to that seen in other real-world studies (**NACASY, KYONAL**)[1–3]
- **Clinically important improvements** were demonstrated in[1]
  - **Bowel function** (Bowel Function Index questionnaire)
  - **Constipation symptoms** (PAC-SYM)
  - **Quality of life** (PAC-QOL)
- OIC must be taken into account as one of the factors that can **decrease quality of life** or **compromise analgesic strategy**[1]
- Potential occurrence of **OIC** should be **considered** from **start of opioid treatment** in cancer patients[1]

OIC, opioid induced constipation; PAC-SYM, Patient Assessment of Constipation Symptoms; PAC-QOL, Patient Assessment of Constipation Quality of Life Questionnaire

1. Lemaire, A, *et al. Supp Care Cancer* 2021;29:7577; 2. Davies, A, *et al. Cancers* 2022;14:1128. 3. Cobo, Dols M, *et al. BMJ Support Palliat Care* 2021 11;25.

Thank you

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PRESCRIBING INFORMATION (prepared August 2021)

Moventig® (naloxegol oxalate) 12.5mg and 25mg film-coated tablets

Consult Summary of Product Characteristics (SmPC) before prescribing.

Indication: Opioid-induced constipation (OIC) in adult patients who have had an inadequate response to laxative(s) (concurrent OIC symptoms of at least moderate severity while taking at least one laxative class for a minimum of four days during the previous 2 weeks). **Dosage and administration:** Recommended 25 mg once daily. Take on empty stomach at least 30 minutes prior to first meal of day or 2 hours after first meal of day. Crushed tablets can be mixed with water (120ml) and drunk immediately or administered via a nasogastric tube (CH8 or greater). **Renal impairment:** Moderate or severe renal impairment starting dose 12.5mg. Discontinue if side effects impact tolerability. Increase to 25mg if well tolerated. **Hepatic impairment:** Use in severe hepatic impairment not recommended. **Moderate CYP3A4 inhibitors:** Starting dose 12.5mg, can be increased to 25mg if well tolerated. **Paediatric population (<18 years):** Safety and efficacy not yet established. **Adverse effects:** Consult SmPC for full list of side effects. Very Common: Abdominal pain, diarrhoea. Common: Nasopharyngitis, headache, flatulence, nausea, vomiting, hyperhidrosis. Uncommon: Opioid withdrawal syndrome. Not known: Hypersensitivity, Gastrointestinal perforation. **Contraindications:** Hypersensitivity to active substance or any of the excipients or any other opioid antagonist. Patients with known or suspected gastrointestinal (GI) obstruction or patients at increased risk of recurrent obstruction. Patients with underlying cancer who are at heightened risk of GI perforation, such as those with underlying malignancies of gastrointestinal tract or peritoneum, recurrent or advanced ovarian cancer or vascular endothelial growth factor (VEGF) inhibitor treatment. Concomitant use with strong CYP3A4 inhibitors. **Warnings and precautions:** Cases of gastrointestinal perforation have been reported in the post-marketing setting, including fatal cases when naloxegol was used in patients who wereat an increased risk of gastrointestinal (GI) perforation. Naloxegol must not be used in patients with known or suspected gastrointestinal obstruction or in patients at increased risk of recurrent obstruction. Use with caution in patients with any condition which might result in impaired integrity of the gastrointestinal tract wall. Advise patients to discontinue therapy and promptly report if unusually severe or persistent abdominal pain develops. Use with caution in patients with clinically important disruptions to the blood brain barrier and observe for potential CNS effects. Discontinue if interference with opioid- mediated analgesia or opioid withdrawal syndrome occurs. Use with caution in patients taking methadone. If opioid withdrawal syndrome is suspected the patient should discontinue Moventig and contact their physician. Use with caution in patients with a recent history of myocardial infarction, symptomatic congestive heart failure, overt cardiovascular (CV) disease or with a QT interval of ≥500msec. Use with caution in OIC patients with cancer-related pain. Use of naloxegol with another opioid antagonist (e.g. naltrexone, naloxone) should be avoided. **Use in pregnancy and lactation:** Not recommended. **Legal category:** POM. **Marketing Authorisation numbers:** Moventig 12.5mg and 25mg tablets (ROI: EU/1/14/962/001-011),(GB: PL GB 50262/004&5) **Further information available on request from the Marketing Authorisation holder:**Kyowa Kirin Holdings B.V., Bloemlaan 2, 2132NP Hoofddorp,The Netherlands.

For the United Kingdom:

NHS cost: Moventig 12.5mg, 30 tablets, £55.20; Moventig 25mg, 30 tablets, £55.20.

Adverse Events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard. Adverse Events should also be reported to Kyowa Kirin Ltd. on +44(0)1896 664000, email medinfo@kyowakirin.com

For the Republic of Ireland

Adverse Events should be reported. Information about adverse event reporting can be found at www.hpra.ie. Adverse Events should also be reported to Kyowa Kirin Ltd. on +44 (0)1896 664000, email medinfo@kyowakirin.com

General considerations for the management of pain with any medication that contains an opioid mechanism of action

The following general aspects should be considered:

- An individualized, patient-centered approach for the diagnosis and treatment of pain is essential to establish a therapeutic alliance between patient and clinician.
- Consider patient variables that may affect opioid dose for each patient prior to opioid use[1]
- In patients with acute pain e.g. post-surgery pain, the use of medication should be for the shortest necessary time[1]. All patients should be carefully selected, addiction risk factors evaluated and regular monitoring and follow-up implemented to ensure that opioids are used appropriately[3-4] and in alignment with treatment goals (pain intensity and functionality) as agreed with the patient[3-4]
- Patients should be made aware of the potential side effects of opioids and the potential for developing tolerance, dependence and addiction[3-4].
- It is important to optimally use multimodal, non-opioid approaches in acute and chronic pain before escalating to opioids or in conjunction with opioid therapy[1]
- Addiction is possible even when opioids are taken as directed. The exact prevalence of addictive disorders in patients treated with opioids for chronic pain is difficult to determine[5]
- Regular clinical reviews are required for long-term opioid treatment to assess pain control, impact on lifestyle, physical and psychological well-being, side effects and continued need for treatment[2]
- Any long term treatment with opioids should be monitored and re-evaluated regular incl. tapering down the dose or discontinuing treatment[3-4]
- Signs of opioid use disorder should be monitored and addressed[3-4]
- Patients and the general public can benefit from clear educational materials and awareness interventions to support the responsible use of opioids[6].

References:

1. DHHS Pain Management Best Practices Inter-Agency Taskforce Report May 2019
2. O'Brien T et al. Eur J Pain 2017;21:3-192
3. Faculty of Pain Medicine, Opioids Aware **https://www.rcoa.ac.uk/faculty-of-pain-medicine/opioids-aware** Accessed September 2019
4. Kosten TR et al, Scie Pract. Perspect 2002;1:13-20
5. Rosenblum A et al Exp. Clin. Psychopharmacol. 2008;16(5):405-416
6. OECD Health Policy. Addressing Problematic opioid use in OECD Countries May2019
   http://www.oecd.org/health/addressing-problematic-opioid-use-in-oecd-countries-a18286f0-en.htm