Naloxegol in opioid-induced constipation: one year of real-world data in patients with cancer

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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

Grünenthal Meds

KKI/INT/MOV/0112. Date of preparation: July 2023.

Introduction on OIBD & OIC

- **OIBD is a common complication of opioid therapy** encompassing a spectrum of symptoms including nausea, vomiting, bloating, gastro-oesophageal reflux-related symptoms and constipation[1-3]
- **OIC** is the **most common subtype of OIBD** for patients receiving opioids[1,4-6]
- OIC occurs in:[1]
  - **51–87% of patients** receiving opioids for **cancer pain**
  - **41–57% of patients** receiving opioids for **chronic non-cancer pain**
- Unlike other adverse effects of opioids, which diminish over time (e.g. nausea, vomiting, sedation), **OIC can persist** throughout the entire treatment period[7-9]

OIBD, opioid-induced bowel dysfunction; OIC, opioid induced constipation

1. Farmer A D, et al. *United European Gastroenterol J.* 2019;7:7–20; 2. Ketwaroo GA, et al. *Curr Gastroenterol Rep* 2013;15:344; 3. Brock C, et al. *Drugs* 2012;72:1847–65; 4. Glare P, et al. *Am J Hosp Palliat Care* 2006;23:229–35; 5.Tuteja AK, et al. *Neurogastroenterol Motil* 2010;22:424–30; 6. Drewes AM, et al. *Scand J Pain* 2016;11:111–22; 7. Cobo Dols M, Beato Zambrano C, Cabezon-Gutierrez L, *et al*. *BMJ Supportive & Palliative Care* Epub ahead of print: March 2021. doi:10.1136/bmjspcare-2020-002816; 8. Bell TJ, et al. Pain Med. 2009;10:35–42; 9. Emmanuel A, et al. Pain Med. 2017;18:1932–1940

Multifaceted impact of OIC

- Constipation has a **considerable negative impact on quality of life** and is associated with **lower work productivity** and **increased healthcare utilisation**[1-4]
- A **recent study (StOIC 1)** has demonstrated the **statistically significant impact of the multifaceted symptoms associated with OIC** in adult patients with cancer pain treated with opioids[5*]:
  - **Other GI** symptoms ($p<0.001$): lack of appetite, nausea, vomiting, feeling bloated, difficulty swallowing
  - **Systemic** symptoms ($p<0.001$): lack of energy, difficulty sleeping, sweats, problems with urination and sexual interest/activity
  - **CNS** symptoms ($p<0.001$): difficulty concentrating
  - **Psychological** symptoms: worrying ($p=0.002$), feeling irritable ($p=0.001$)
- Lifestyle adaptations, laxatives and opioid dose reductions are often ineffective at relieving OIC. This can lead to opioid treatment discontinuation, resulting in **inadequate pain management**[1-3]

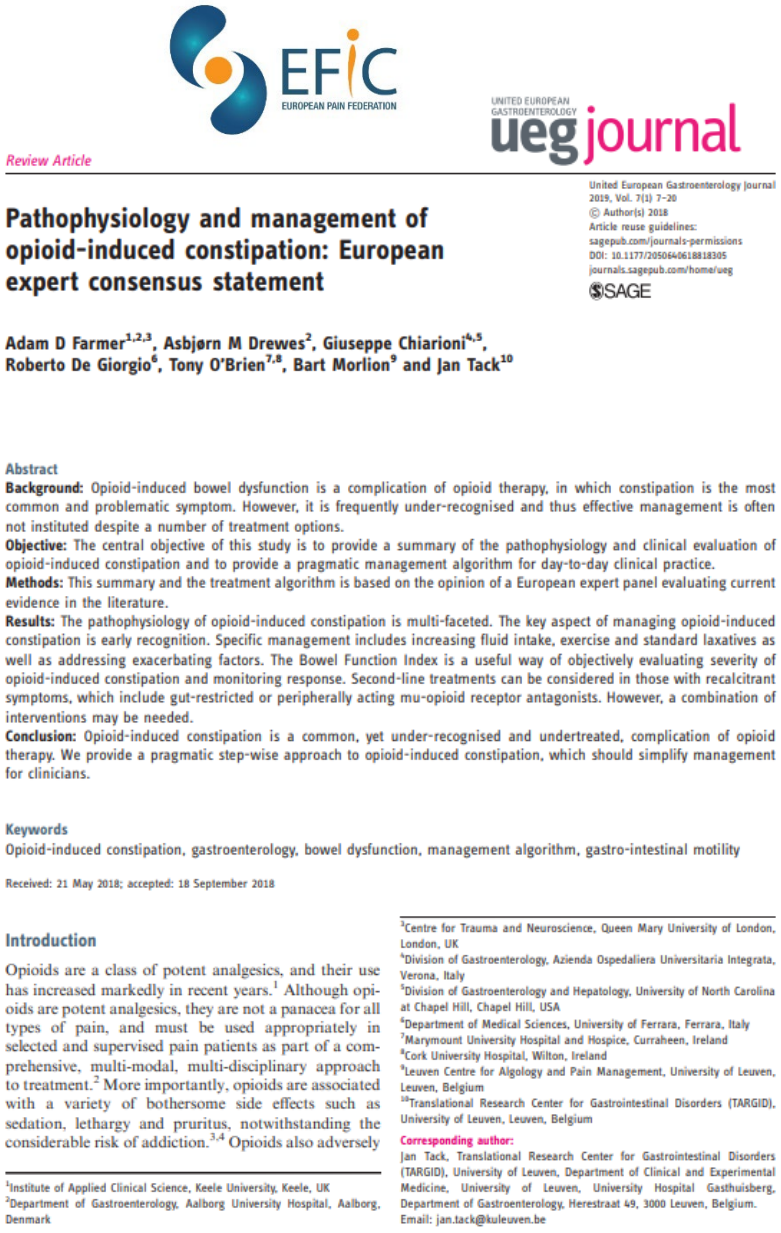
OIC, opioid induced constipation; StOIC, Study of Opioid-Induced Constipation; GI, gastrointestinal

* As assessed by Memorial Symptom Assessment Scale - Short Form (MSAS-SF) data.

1. Farmer A D, et al. *United European Gastroenterol J.* 2019;7:7–20; 2. Bell TJ, et al. Pain Med. 2009;10:35–42; 3. Emmanuel A, et al. Pain Med. 2017;18:1932–1940; 4. Bell T *et al*. *J Opioid Manag* 2009;5:137–144;
5. Davies A, Leach C, Butler C, Gregory A, Henshaw S, Minton O, Shorthose K, Batsari, K. Opioid-induced constipation in patients with cancer: a "real-world", multicentre, observational study of diagnostic criteria and clinical features, PAIN: January 2021 - Volume 162 - Issue 1 - p 309-318. doi: 10.1097/j.pain.0000000000002024

OIC recognition and diagnosis

- OIC is frequently **under-recognised** and effective management is often **delayed or not instituted**[1,2]
- **Previously a lack of pragmatic guidance** on the management of OIC may have contributed to this under-recognition and sub-optimal management[3]
- The **European Expert Consensus Statement, endorsed by the European Pain Federation[3†]:**
  - First report of its kind, developed by a European expert multidisciplinary panel of 7 specialists (including neuro-gastroenterology, oncology, pain medicine and palliative medicine) with the aim of simplifying the management of OIC for clinicians
  - Provides a summary of OIC pathophysiology, gives guidance on clinical evaluation and a pragmatic step-wise management algorithm suggestion for day-to-day clinical practice



EFIC EUROPEAN PAIN FEDERATION

UNITED EUROPEAN GASTROENTEROLOGY ueg journal

Review Article

United European Gastroenterology Journal 2019, Vol. 7(1) 7–20
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Pathophysiology and management of opioid-induced constipation: European expert consensus statement

Adam D Farmer[1,2,3], Asbjørn M Drewes[2], Giuseppe Chiarioni[4,5], Roberto De Giorgio[6], Tony O'Brien[7,8], Bart Morlion[9] and Jan Tack[10]

Abstract

Background: Opioid-induced bowel dysfunction is a complication of opioid therapy, in which constipation is the most common and problematic symptom. However, it is frequently under-recognised and thus effective management is often not instituted despite a number of treatment options.
Objective: The central objective of this study is to provide a summary of the pathophysiology and clinical evaluation of opioid-induced constipation and to provide a pragmatic management algorithm for day-to-day clinical practice.
Methods: This summary and the treatment algorithm is based on the opinion of a European expert panel evaluating current evidence in the literature.
Results: The pathophysiology of opioid-induced constipation is multi-faceted. The key aspect of managing opioid-induced constipation is early recognition. Specific management includes increasing fluid intake, exercise and standard laxatives as well as addressing exacerbating factors. The Bowel Function Index is a useful way of objectively evaluating severity of opioid-induced constipation and monitoring response. Second-line treatments can be considered in those with recalcitrant symptoms, which include gut-restricted or peripherally acting mu-opioid receptor antagonists. However, a combination of interventions may be needed.
Conclusion: Opioid-induced constipation is a common, yet under-recognised and undertreated, complication of opioid therapy. We provide a pragmatic step-wise approach to opioid-induced constipation, which should simplify management for clinicians.

Keywords
Opioid-induced constipation, gastroenterology, bowel dysfunction, management algorithm, gastro-intestinal motility

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Introduction

Opioids are a class of potent analgesics, and their use has increased markedly in recent years.[1] Although opioids are potent analgesics, they are not a panacea for all types of pain, and must be used appropriately in selected and supervised pain patients as part of a comprehensive, multi-modal, multi-disciplinary approach to treatment.[2] More importantly, opioids are associated with a variety of bothersome side effects such as sedation, lethargy and pruritus, notwithstanding the considerable risk of addiction.[3,4] Opioids also adversely

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OIC, opioid induced constipation

† With permissions from the European Pain Federation (EFIC).

1. Ducrotté P, et al. *United European gastroenterology journal*, 2017; 2. Gupta A. et al. *Pain Med.* 2018: 3. Farmer A D, et al. *United European Gastroenterol J.* 2019;7:7–20.

European Expert Consensus Statement – Treatment Algorithm[1†]

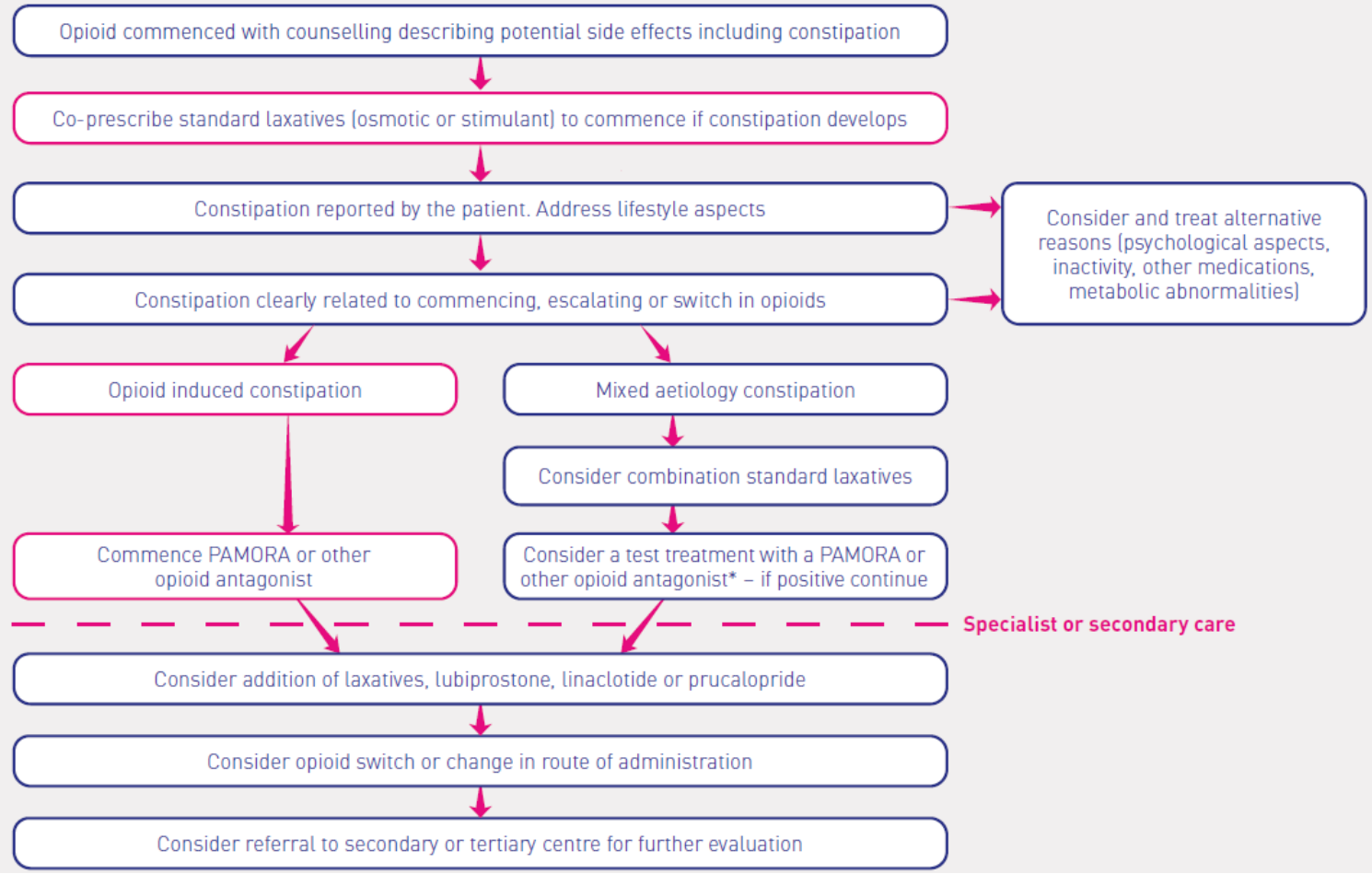


Illustration adapted Farmer A D, et al. *United European Gastroenterol J.* 2019;7:7–20.

OIC, opioid induced constipation

† With permissions from the European Pain Federation (EFIC).

1. Farmer A D, et al. *United European Gastroenterol J.* 2019;7:7–20.

* The length of the test treatment depends on the specific PAMORA or opioid antagonist. For instance, a two-week trial with naloxegol or a single test dose with subcutaneous methylnaltrexone may be appropriate. Following these pragmatic suggestions is dependent on cost, available expertise/technology and local practice circumstances.

KYONAL study: introduction

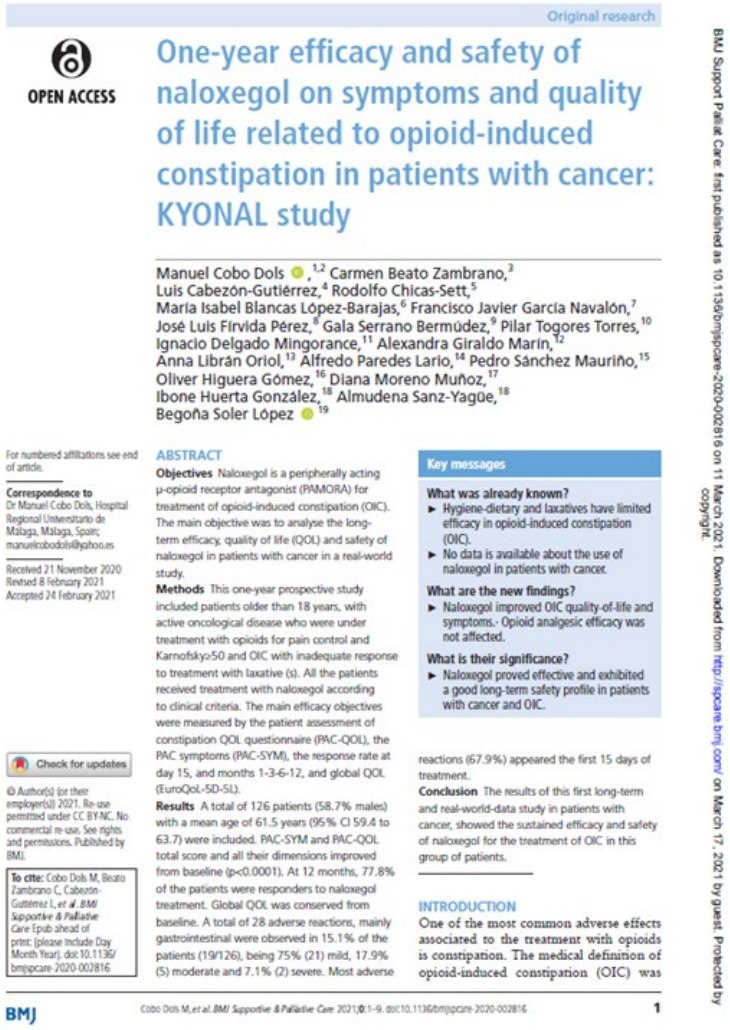
- Naloxegol was the first oral PAMORA indicated for treatment of OIC in adult patients who have had an inadequate response to laxative(s)[1]
- The **objective of the KYONAL study** was to analyse the **long-term efficacy, quality of life and safety of naloxegol** in patients with cancer and OIC in a **real-world** study lasting twelve months[2]
- The **primary efficacy endpoint** was to assess the impact of naloxegol on constipation-related **quality of life**[2]
- The KYONAL study protocol required patients to be treated according to the Moventig (naloxegol) SmPC

PAMORA, peripherally acting μ-opioid receptor antagonist; OIC, opioid-induced constipation; SmPC, summary of product characteristics

1. **MOVENTIG** Summary of Product Characteristics.
2. Cobo Dols M, Beato Zambrano C, Cabezon-Gutierrez L, *et al. BMJ Supportive & Palliative Care* Epub ahead of print: March 2021. doi:10.1136/bmjspcare-2020-002816

KYONAL: 12-Month Results

KYONAL: 12-month results[1]



Original research

OPEN ACCESS

One-year efficacy and safety of naloxegol on symptoms and quality of life related to opioid-induced constipation in patients with cancer: KYONAL study

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ABSTRACT

Objectives Naloxegol is a peripherally acting μ-opioid receptor antagonist (PAMORA) for treatment of opioid-induced constipation (OIC). The main objective was to analyse the long-term efficacy, quality of life (QOL) and safety of naloxegol in patients with cancer in a real-world study.

Methods This one-year prospective study included patients older than 18 years, with active oncological disease who were under treatment with opioids for pain control and Karnofsky≥50 and OIC with inadequate response to treatment with laxative (s). All the patients received treatment with naloxegol according to clinical criteria. The main efficacy objectives were measured by the patient assessment of constipation QOL questionnaire (PAC-QOL), the PAC symptoms (PAC-SYM), the response rate at day 15, and months 1-3-6-12, and global QOL (EuroQoL-5D-5L).

Results A total of 126 patients (58.7% males) with a mean age of 61.5 years (95% CI 59.4 to 63.7) were included. PAC-SYM and PAC-QOL total score and all their dimensions improved from baseline ($p<0.0001$). At 12 months, 77.8% of the patients were responders to naloxegol treatment. Global QOL was conserved from baseline. A total of 28 adverse reactions, mainly gastrointestinal were observed in 15.1% of the patients (19/126), being 75% (21) mild, 17.9% (5) moderate and 7.1% (2) severe. Most adverse reactions (67.9%) appeared the first 15 days of treatment.

Conclusion The results of this first long-term and real-world-data study in patients with cancer, showed the sustained efficacy and safety of naloxegol for the treatment of OIC in this group of patients.

Key messages

What was already known?
- Hygiene-dietary and laxatives have limited efficacy in opioid-induced constipation (OIC).
- No data is available about the use of naloxegol in patients with cancer.

What are the new findings?
- Naloxegol improved OIC quality-of-life and symptoms.· Opioid analgesic efficacy was not affected.

What is their significance?
- Naloxegol proved effective and exhibited a good long-term safety profile in patients with cancer and OIC.

INTRODUCTION

One of the most common adverse effects associated to the treatment with opioids is constipation. The medical definition of opioid-induced constipation (OIC) was

1. Cobo Dols M, Beato Zambrano C, Cabezon-Gutierrez L, *et al*. *BMJ Supportive & Palliative Care* Epub ahead of print: March 2021. doi:10.1136/bmjspcare-2020-002816

KYONAL: study summary[1]

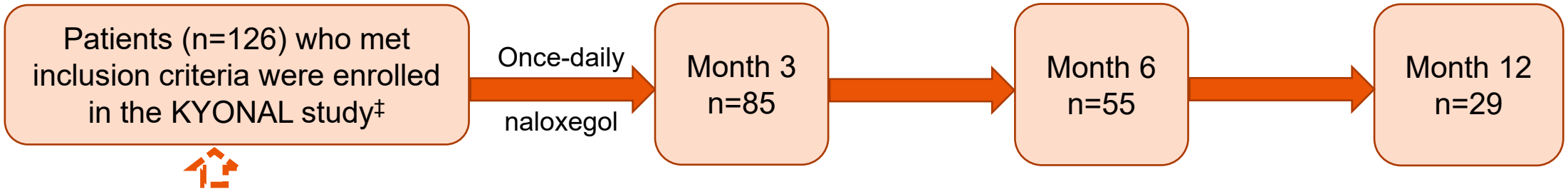
- Spanish, 12-month follow-up real-world study in adult patients with cancer and opioid induced constipation with an inadequate response to laxative
- Primary endpoint: assessment of constipation-related quality of life in patients receiving naloxegol
- Secondary endpoints: evaluation of the efficacy of naloxegol in treating OIC
- Total of 126 patients included and treated according to the naloxegol SmPC, in line with the KYONAL study protocol

SmPC: Summary of Product Characteristics

1. Cobo Dols M, Beato Zambrano C, Cabezon-Gutierrez L, *et al*. *BMJ Supportive & Palliative Care* Epub ahead of print: March 2021. doi:10.1136/bmjspcare-2020-002816

KYONAL: study design[1]

- KYONAL was a 12-month prospective observational follow-up study in 16 departments of medical oncology (12), palliative care units (2), radiation oncology (2)



Key inclusion criteria:
- Outpatients >18 years old
- Active oncological disease requiring opioid treatment for pain control
- Symptoms of OIC* at screening
- Inadequate response to laxatives** and indication for naloxegol
- Karnofsky performance status score ≥50 at study entry

- Naloxegol was administered to eligible patients at a starting dose of 12.5 mg (11.1%; n=14) or 25 mg (88.1%; n=111)†
- Follow-up visits and symptom assessment at 15 days, 1 month, 3 months, 6 months and 12 months

* OIC definition based on Rome IV criteria (average <3 spontaneous bowel movements a week with associated symptoms of constipation in ≥25% of the bowel movements).
** Inadequate response to laxatives defined as patients reporting symptoms of OIC for at least 4 days in the 2 weeks prior to the study while receiving treatment with at least one class of laxatives.
‡ The intent-to-treat rules were applied to the analyses of response to treatment, PAC-QOL, PAC-SYM and pain intensity as efficacy variables using the last observation carried forward (LOCF) method for imputation of missing data in patients lost to follow-up.
† One patient was on a dose of 6.25 mg/day. OIC, opioid-induced constipation.

1. Cobo Dols M, Beato Zambrano C, Cabezon-Gutierrez L, *et al*. *BMJ Supportive & Palliative Care* Epub ahead of print: March 2021. doi:10.1136/bmjspcare-2020-002816

KYONAL: selected baseline demographics[1] (1/3)

- The most commonly used opioids at inclusion were:
  - Fentanyl: 58.7% (n=74)
  - Morphine: 26.2% (n=33)
  - Methadone: 0.8% (n=1)
  - Oxycodone: 11.9% (n=15)
  - Tapentadol: 2.4% (n=3)
- Main cause of pain was cancer (88.9%; n=112)
- Time from cancer diagnosis: 34.7 months [95% CI: 23.5-45.9]
- Presence of metastases: 67.5% (n=85)

CI, confidence interval

1. Cobo Dols M, Beato Zambrano C, Cabezon-Gutierrez L, *et al*. *BMJ Supportive & Palliative Care* Epub ahead of print: March 2021. doi:10.1136/bmjspcare-2020-002816

KYONAL: selected baseline demographics[1] (2/3)

64.3% of patients (n=81) were **receiving treatment for some comorbid condition** at study entry

27.8% of patients (n=35) had a **prior history of constipation**

Patients **experienced OIC** for an **average of 3.1 months** [95% CI 2.0–4.2]

CI, confidence interval; OIC, opioid-induced constipation

1. Cobo Dols M, Beato Zambrano C, Cabezon-Gutierrez L, *et al*. *BMJ Supportive & Palliative Care* Epub ahead of print: March 2021. doi:10.1136/bmjspcare-2020-002816

KYONAL: selected baseline demographics[1] (3/3)

Demographics	% (n) or mean [95% CI] n=126
Age	61.5 [59.4–63.7]
Gender	
Male	58.7 (74)
Female	41.3 (52)
Race	
Caucasian	99.2 (125)
Black	0.8 (1)
Socioeconomic level	
Low	17.5 (22)
Middle	71.4 (90)
High	11.1 (14)
Body mass index, kg/m^2	25.0 [24.2–25.8]
Karnofsky performance status (%)	77.5 [75.4–79.7]

CI, confidence interval

1. Cobo Dols M, Beato Zambrano C, Cabezon-Gutierrez L, *et al*. *BMJ Supportive & Palliative Care* Epub ahead of print: March 2021. doi:10.1136/bmjspcare-2020-002816

KYONAL[1]

		% (n) or median [95% CI]
Main reason for using opioids	Cancer	88.9% (112)
Opioids administered for the treatment of pain (one or several treatments)	Fentanyl Morphine Oxycodone Tapentadol Methadone	58.7% (74) 26.2% (33) 11.9% (15) 2.4% (3) 0.8% (1)
Mean time since OIC diagnosis		3.1 months [95% CI 2.0 – 4.2]
Previous key treatments for OIC (one or several)	Macrogol Lactulose Bisacodyl Paraffin oil Magnesia	31.0% (39) 30.2% (38) 8.7% (11) 4.0% (5) 4.0% (5)

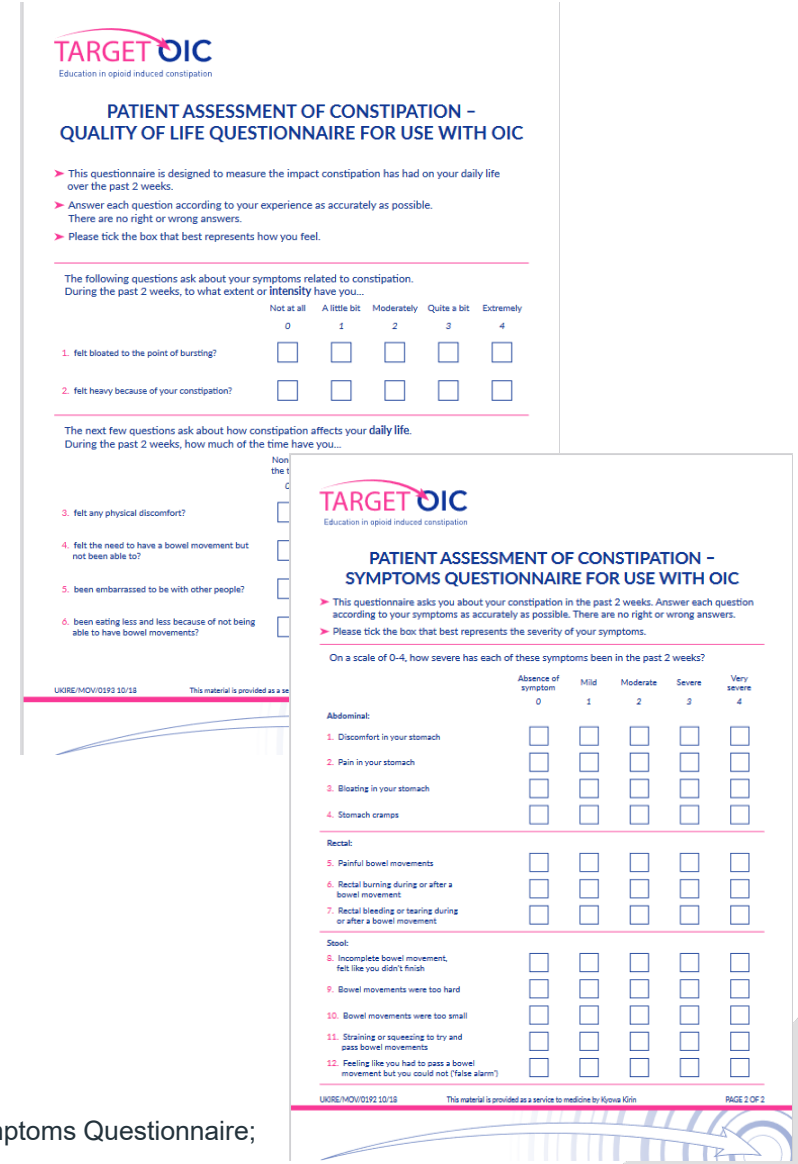
- 27.8% (n=35) with **history of constipation prior to OIC**
- 48.4% (n=61) of patients received **concomitant laxative treatment** along with naloxegol
- **Baseline:**
  - 61.1% (n=77) on **chemotherapy**
  - 84.9% (n=107) on **other pharmaceutical treatments which can induce constipation**

CI, confidence interval; OIC, opioid induced constipation

1. Cobo Dols M, Beato Zambrano C, Cabezon-Gutierrez L, *et al*. *BMJ Supportive & Palliative Care* Epub ahead of print: March 2021. doi:10.1136/bmjspcare-2020-002816

PAC-QOL & PAC-SYM questionnaires additional information[1]

- PAC-QOL: 28 questions on quality of life (QoL), with scores 0-4 and four domains:
  - Worries and concerns
  - Physical discomfort
  - Psychosocial discomfort
  - Satisfaction
- PAC-SYM: 12 questions on efficacy, with scores 0-4 and three domains:
  - Abdominal symptom
  - Rectal symptom
  - Stool symptom
- For both PAC-QOL and PAC-SYM, changes in total or subscale scores of ≥ 0.5 points considered clinically relevant
- Lower score = better QoL (PAC-QOL) / more efficacy (PAC-SYM)


TARGET OIC
Education in opioid induced constipation

PATIENT ASSESSMENT OF CONSTIPATION – QUALITY OF LIFE QUESTIONNAIRE FOR USE WITH OIC

- This questionnaire is designed to measure the impact constipation has had on your daily life over the past 2 weeks.
- Answer each question according to your experience as accurately as possible. There are no right or wrong answers.
- Please tick the box that best represents how you feel.

The following questions ask about your symptoms related to constipation.
During the past 2 weeks, to what extent or **intensity** have you...

	Not at all 0	A little bit 1	Moderately 2	Quite a bit 3	Extremely 4
1. felt bloated to the point of bursting?	☐	☐	☐	☐	☐
2. felt heavy because of your constipation?	☐	☐	☐	☐	☐

The next few questions ask about how constipation affects your **daily life**.
During the past 2 weeks, how much of the time have you...

	Non the t 0
3. felt any physical discomfort?	☐
4. felt the need to have a bowel movement but not been able to?	☐
5. been embarrassed to be with other people?	☐
6. been eating less and less because of not being able to have bowel movements?	☐

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TARGET OIC
Education in opioid induced constipation

PATIENT ASSESSMENT OF CONSTIPATION – SYMPTOMS QUESTIONNAIRE FOR USE WITH OIC

- This questionnaire asks you about your constipation in the past 2 weeks. Answer each question according to your symptoms as accurately as possible. There are no right or wrong answers.
- Please tick the box that best represents the severity of your symptoms.

On a scale of 0-4, how severe has each of these symptoms been in the past 2 weeks?

	Absence of symptom 0	Mild 1	Moderate 2	Severe 3	Very severe 4
Abdominal:					
1. Discomfort in your stomach	☐	☐	☐	☐	☐
2. Pain in your stomach	☐	☐	☐	☐	☐
3. Bloating in your stomach	☐	☐	☐	☐	☐
4. Stomach cramps	☐	☐	☐	☐	☐
Rectal:					
5. Painful bowel movements	☐	☐	☐	☐	☐
6. Rectal burning during or after a bowel movement	☐	☐	☐	☐	☐
7. Rectal bleeding or tearing during or after a bowel movement	☐	☐	☐	☐	☐
Stool:					
8. Incomplete bowel movement, felt like you didn't finish	☐	☐	☐	☐	☐
9. Bowel movements were too hard	☐	☐	☐	☐	☐
10. Bowel movements were too small	☐	☐	☐	☐	☐
11. Straining or squeezing to try and pass bowel movements	☐	☐	☐	☐	☐
12. Feeling like you had to pass a bowel movement but you could not ('false alarm')	☐	☐	☐	☐	☐

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PAC-QOL, Patient Assessment of Constipation Quality of Life Questionnaire; PAC-SYM, Patient Assessment of Constipation Symptoms Questionnaire; QoL: quality of life

1. Cobo Dols M, Beato Zambrano C, Cabezon-Gutierrez L, *et al*. *BMJ Supportive & Palliative Care* Epub ahead of print: March 2021. doi:10.1136/bmjspcare-2020-002816

KYONAL: study objectives[1]

Primary objective: PAC-QOL* (4 dimensions)

Physical discomfort	Psychosocial discomfort	Worries and concerns	Satisfaction

Secondary objective: PAC-SYM* (3 dimensions)

Abdominal symptoms	Rectal symptoms	Stool symptoms

Secondary objective: efficacy (response rate)

Response: ≥3 spontaneous bowel movements AND an increase of ≥1 spontaneous bowel movements over baseline

Secondary objective: safety (adverse events)

Grading: 0 (less severe) to 4 (more severe)
Over the previous 2 weeks

Clinical relevance: change of ≥0.5 points

Lower score = improvement in QoL / symptoms

Patients recorded the number of weekly bowel movements, the use of rescue medication, changes in pain treatments and adverse reactions

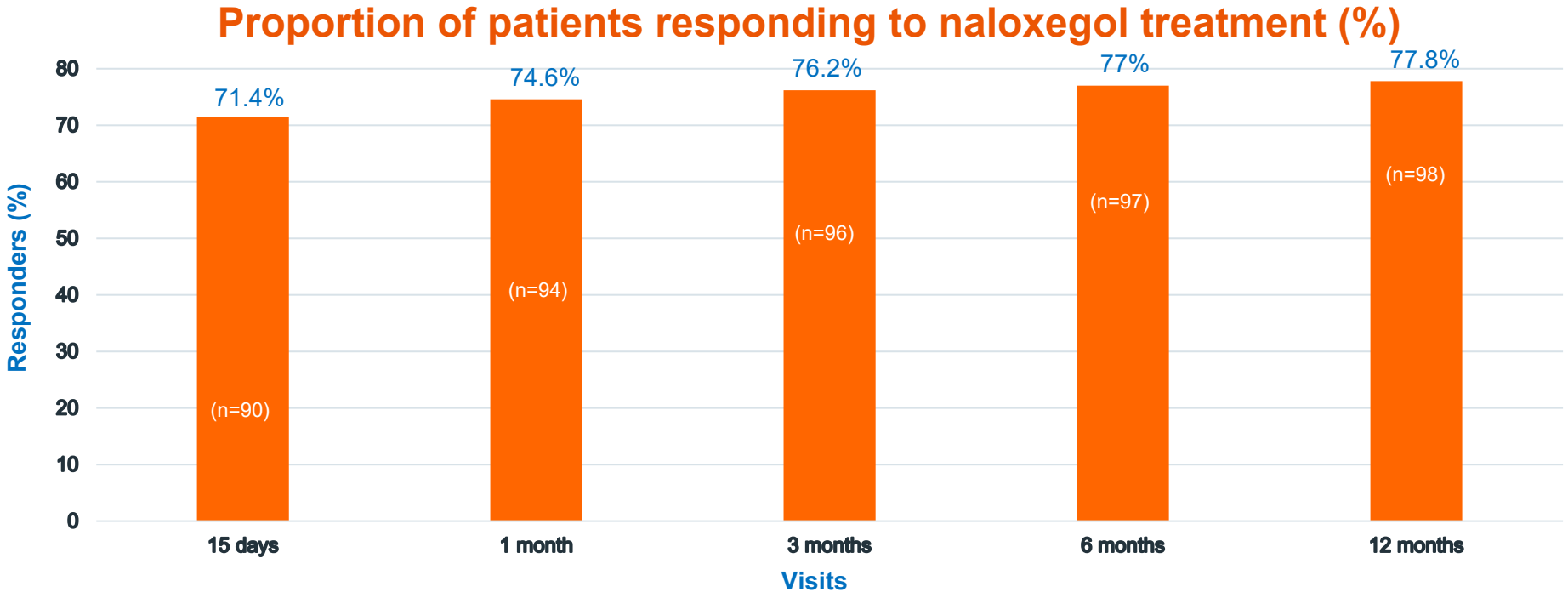
- **Pain intensity assessment**: 10-point VAS (0=no pain; 10=maximum pain)
- **Mean stool consistency**: 7-point Bristol scale

PAC-QOL, Patient Assessment of Constipation Quality of Life Questionnaire; PAC-SYM, Patient Assessment of Constipation Symptoms Questionnaire; VAS, Visual Analogue Scale; QoL, quality of life

*Validated Spanish versions. An intent-to-treat analysis was performed for primary and secondary outcomes.

1. Cobo Dols M, Beato Zambrano C, Cabezon-Gutierrez L, *et al*. *BMJ Supportive & Palliative Care* Epub ahead of print: March 2021. doi:10.1136/bmjspcare-2020-002816

At 12 months, 77.8% (n=98) of patients were **responders** to naloxegol treatment[1]



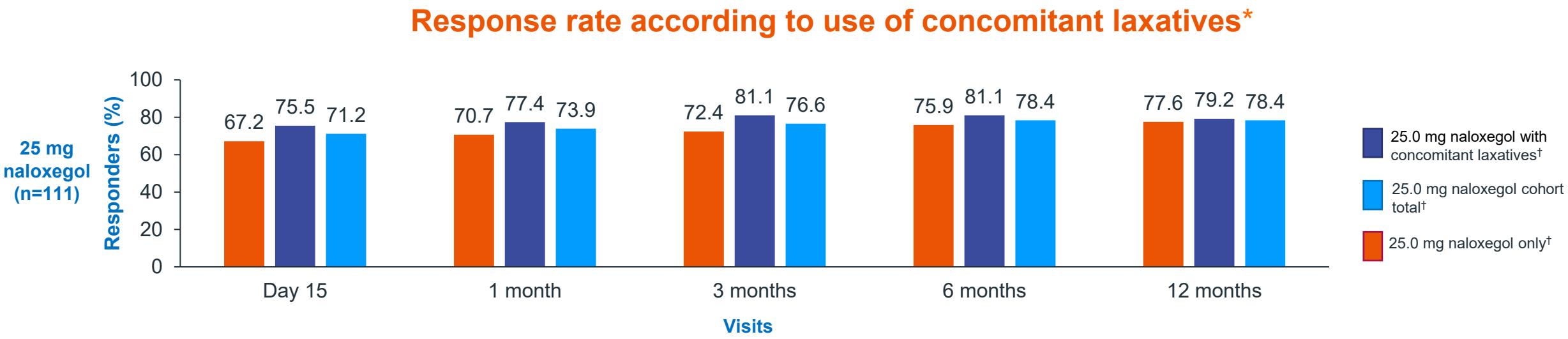
- Sustained increase in response rate between Day 15 (71.4%, n=90 [95% CI 62.7-79.1]) and Month 12 (77.8%, n=98 [95% CI 69.5-84.7])
- No significant differences in response to treatment according to patient's baseline characteristics

Statistical assessment of response rates consisted of an intent-to-treat (ITT) analysis utilising the "last observation carried forward". Response was defined as ≥3 spontaneous bowel movements AND an increase of ≥1 spontaneous bowel movements over baseline.

CI, confidence interval

1. Cobo Dols M, Beato Zambrano C, Cabezon-Gutierrez L, *et al*. *BMJ Supportive & Palliative Care* Epub ahead of print: March 2021. doi:10.1136/bmjspcare-2020-002816

No significant response rate differences by use of concomitant laxative treatment[1]



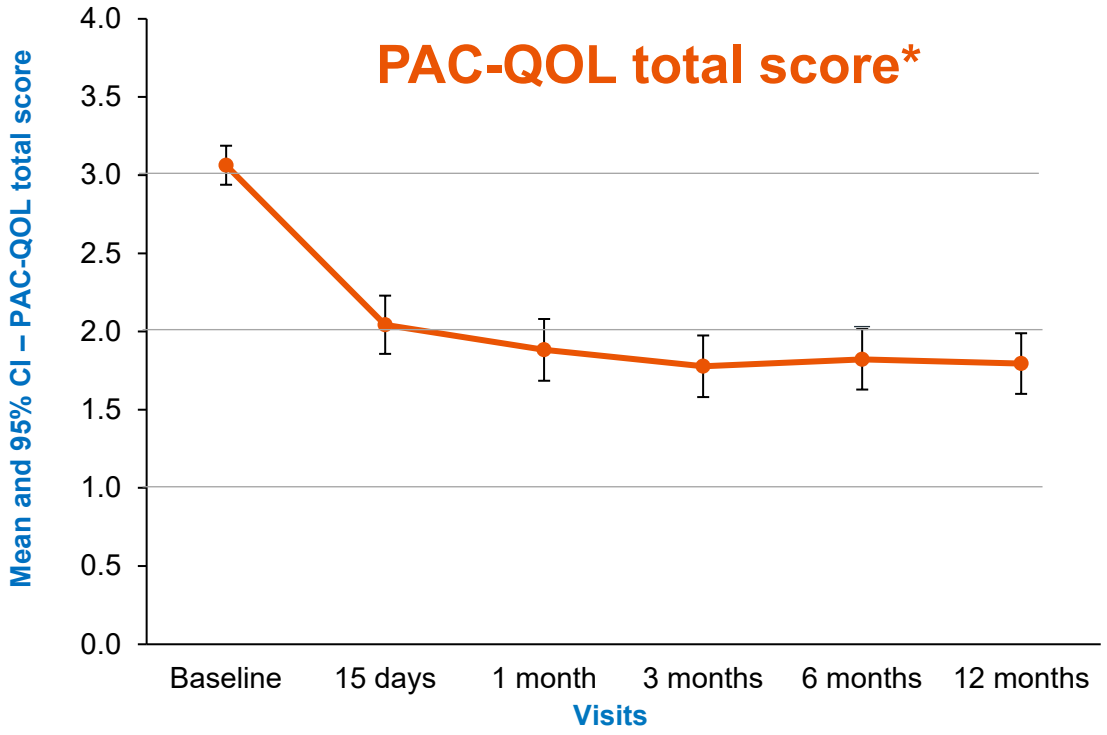
- The response to naloxegol 25mg treatment was maintained over 12 months, with 78.4% of patients responding to naloxegol 25mg treatment (with and without concomitant laxatives)
- The authors also reported no significant response rate differences by dose

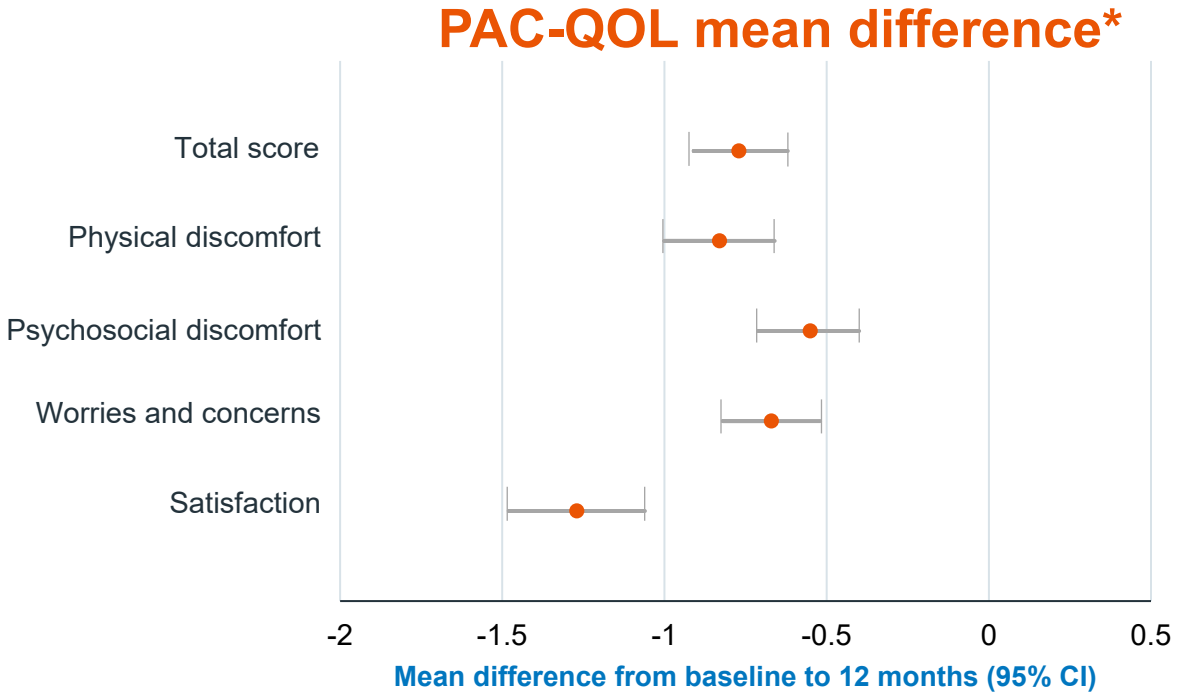
Statistical assessment of response rates consisted of an intent-to-treat (ITT) analysis utilising the “last observation carried forward”. Response was defined as ≥3 spontaneous bowel movements AND an increase of ≥1 spontaneous bowel movements over baseline.

* Visual adapted from publication; † One patient received a naloxegol dose of 6.25 mg

1. Cobo Dols M, Beato Zambrano C, Cabezon-Gutierrez L, *et al*. *BMJ Supportive & Palliative Care* Epub ahead of print: March 2021. doi:10.1136/bmjspcare-2020-002816

Naloxegol administration resulted in clinically and statistically significant improvements in PAC-QOL scores[1]





- **PAC-QOL total score and scores for each of the 4 dimensions significantly improved from baseline to 12-month follow-up (p<0.0001)**
- **58.7% (n=74) of patients showed clinically relevant improvements in total PAC-QOL score at month 12**
- **Largest improvement in 'patient satisfaction' dimension of PAC-QOL: three times greater than improvement in other subscales**

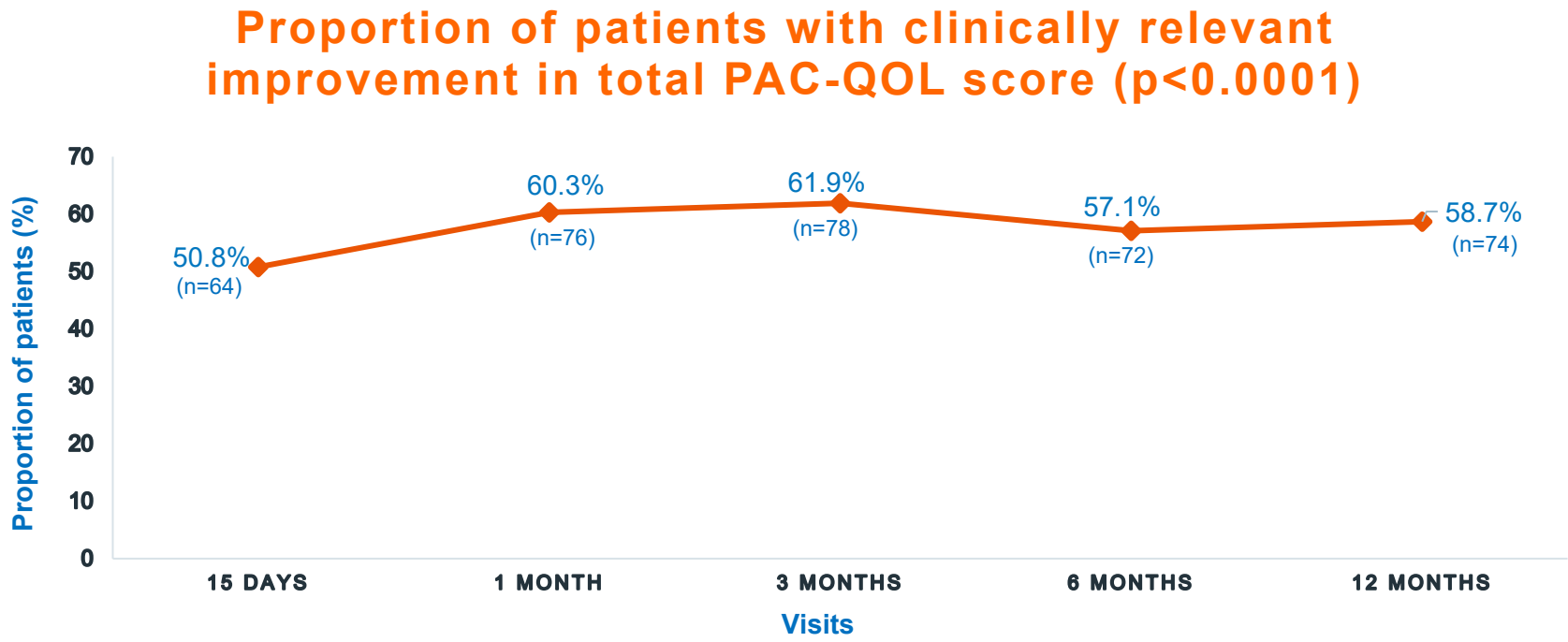
Statistical assessment of response rates consisted of an intent-to-treat (ITT) analysis utilising the "last observation carried forward".

CI, confidence interval; PAC-QOL, Patient Assessment of Constipation Quality of Life Questionnaire: 28 questions on quality of life (scores 0-4) and 4 domains: worries and concerns, physical discomfort, psychosocial discomfort & satisfaction.

* Visual adapted from publication

1. Cobo Dols M, Beato Zambrano C, Cabezon-Gutierrez L, *et al. BMJ Supportive & Palliative Care* Epub ahead of print: March 2021. doi:10.1136/bmjspcare-2020-002816

Clinically and statistically significant improvements (p<0.0001) in PAC-QOL scores between baseline and all subsequent visits[1]



- PAC-QOL total score and all 4 dimensions improved from baseline (p<0.0001)
- The proportion of patients with clinically and statistically significant improvements from baseline in total PAC-QOL score was higher at 12 months [58.7% (n=74)] compared with score at Day 15 [50.8% (n=64)]

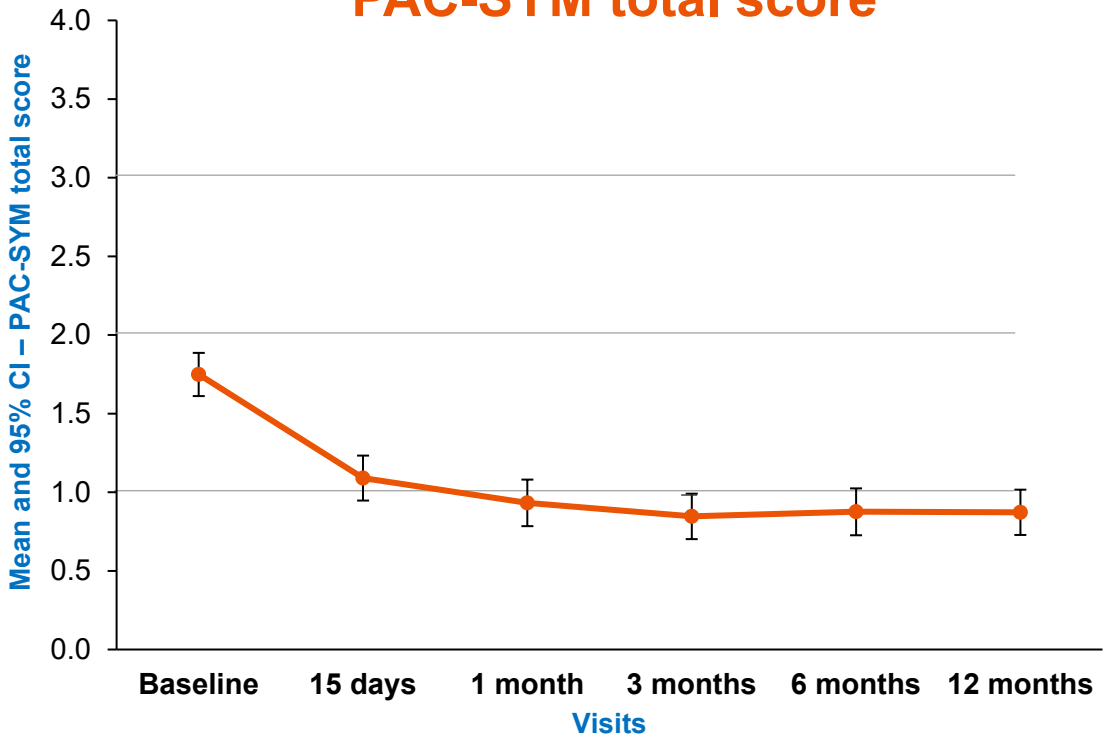
Statistical assessment of response rates consisted of an intent-to-treat (ITT) analysis utilising the “last observation carried forward”.

PAC-QOL, Patient Assessment of Constipation Quality of Life Questionnaire: 28 questions on quality of life (scores 0-4) and 4 domains: worries and concerns, physical discomfort, psychosocial discomfort & satisfaction.

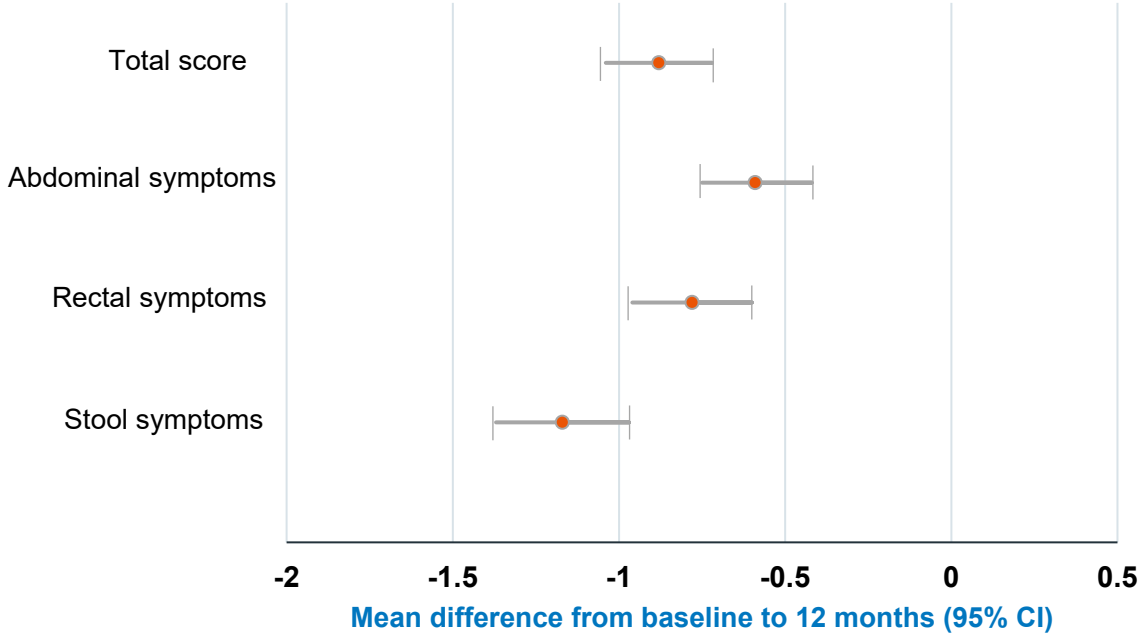
1. Cobo Dols M, Beato Zambrano C, Cabezon-Gutierrez L, *et al*. *BMJ Supportive & Palliative Care* Epub ahead of print: March 2021. doi:10.1136/bmjspcare-2020-002816

Naloxegol administration resulted in clinically and statistically significant improvement in PAC-SYM scores[1]

PAC-SYM total score*



PAC-SYM mean difference*



- **PAC-SYM total score and scores for each of the 3 dimensions significantly improved from baseline to 12-month follow-up (p<0.0001)**
- **65.9% (n=83) of patients showed clinically relevant improvements in total PAC-SYM score at Month 12**

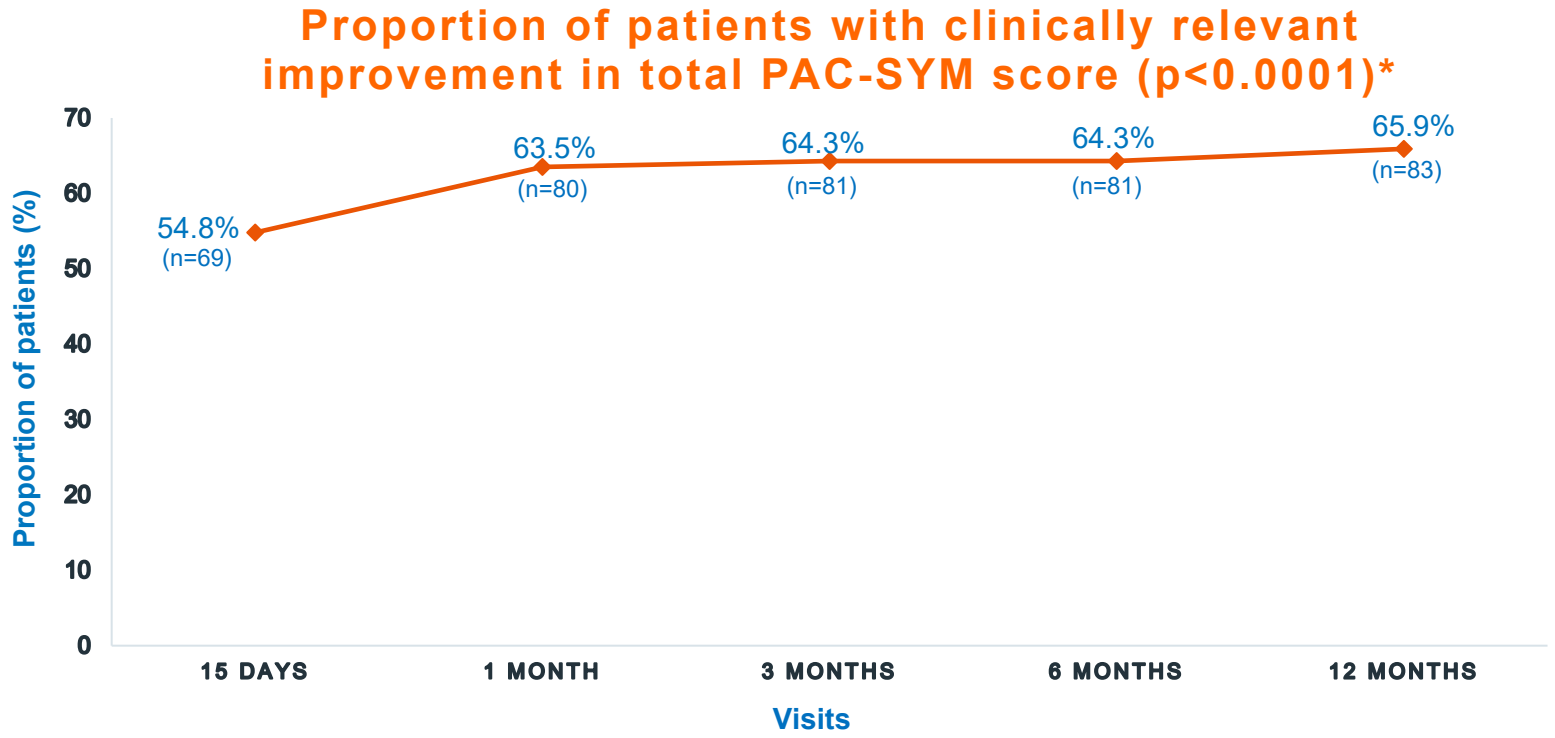
Statistical assessment of response rates consisted of an intent-to-treat (ITT) analysis utilising the “last observation carried forward”.

CI, confidence interval; PAC-SYM, Patient Assessment of Constipation-Symptoms: 12 questions on efficacy (scores 0-4) and 3 domains: abdominal, rectal and stool symptoms.

* Visual adapted from publication

1. Cobo Dols M, Beato Zambrano C, Cabezon-Gutierrez L, *et al*. *BMJ Supportive & Palliative Care* Epub ahead of print: March 2021. doi:10.1136/bmjspcare-2020-002816

Clinically and statistically significant improvement (p<0.0001) in PAC-SYM scores between baseline and all subsequent visits[1]



- **PAC-SYM total score and all 3 dimensions improved from baseline (p<0.0001)**
- **The proportion of patients with clinically meaningful improvements in total PAC-SYM score was higher at 12 months [65.9% (n=83)] compared with visit at Day 15 [54.8% (n=69)]**

Statistical assessment of response rates consisted of an intent-to-treat (ITT) analysis utilising the “last observation carried forward”.

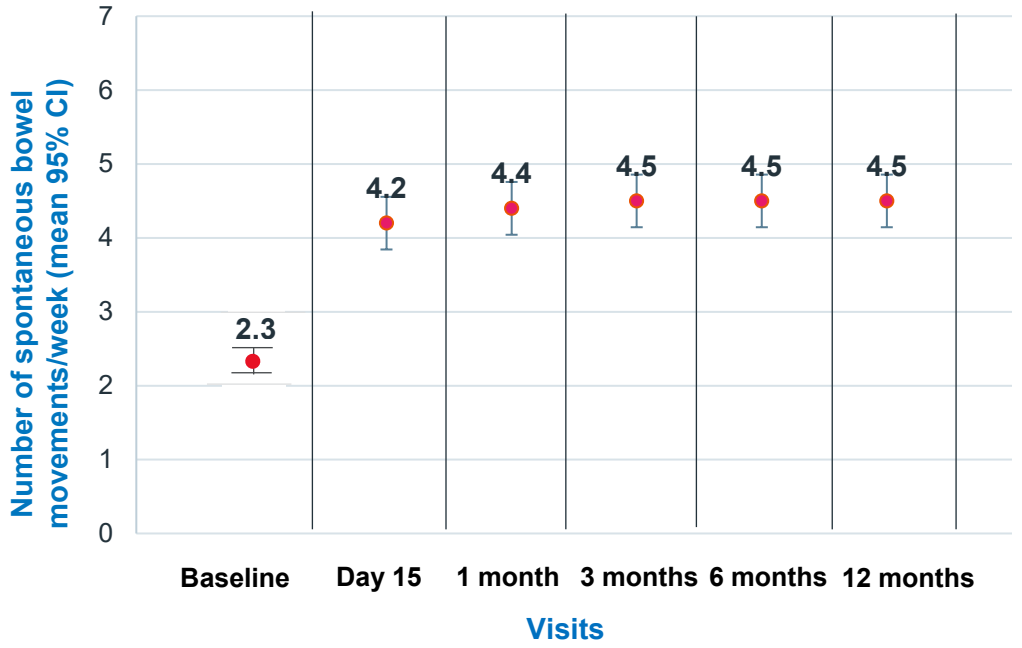
PAC-SYM, Patient Assessment of Constipation-Symptoms: 12 questions on efficacy (scores 0-4) and 3 domains: abdominal, rectal and stool symptoms.

* Visual created from data in publication

1. Cobo Dols M, Beato Zambrano C, Cabezon-Gutierrez L, *et al*. *BMJ Supportive & Palliative Care* Epub ahead of print: March 2021. doi:10.1136/bmjspcare-2020-002816

Statistically significant increase in spontaneous bowel movements from baseline (p<0.0001)[1]

Evolution of stool movements from baseline to Month 12*



- **Statistically significant increase in mean number of days per week with complete SBM from baseline (p<0.0001) at all study visits**
  - **Cancer patients with OIC treated with naloxegol significantly increased SBMs per week from a mean of 2.3 at baseline to a mean of 4.5 at 3 months and this improvement was maintained at Month 12 (p<0.0001)**

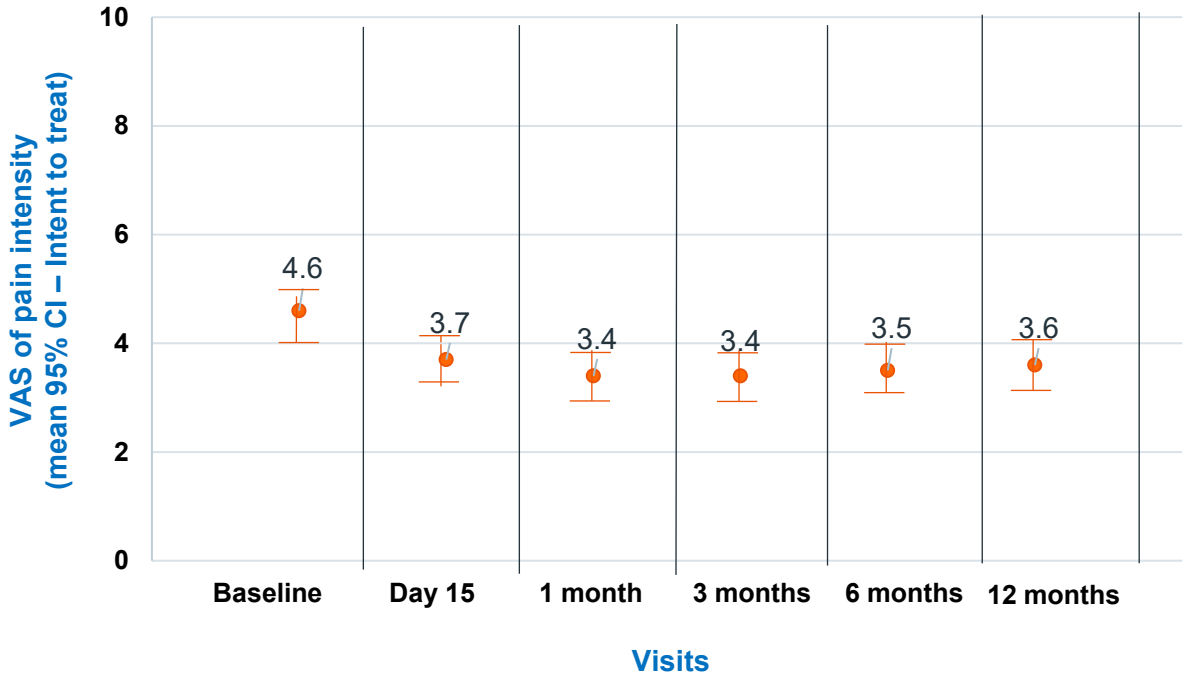
Analysis performed in a per-protocol population. SBM, spontaneous bowel movement

* Visual adapted from publication

1. Cobo Dols M, Beato Zambrano C, Cabezon-Gutierrez L, *et al. BMJ Supportive & Palliative Care* Epub ahead of print: March 2021. doi:10.1136/bmjspcare-2020-002816

Statistically significant decrease in pain intensity between baseline and all visits (p<0.001)[1]

Visual Analogue Scale of pain intensity from baseline to Month 12[1]*



- **VAS scores were maintained under 4 points from Day 15 to Month 12[1]**
- **Naloxegol treatment did not interfere with opioid treatment for pain management in patients with cancer and OIC[1,2]**

Statistical assessment of response rates consisted of an intent-to-treat (ITT) analysis utilising the "last observation carried forward".

VAS, Visual Analogue Scale; CI, confidence interval

* Visual adapted from publication

1. Cobo Dols M, Beato Zambrano C, Cabezon-Gutierrez L, *et al*. *BMJ Supportive & Palliative Care* Epub ahead of print: March 2021. doi:10.1136/bmjspcare-2020-002816;
2. **MOVENTIG** Summary of Product Characteristics.

Adverse reactions[1]

- Adverse reactions were observed in 15.1% of patients (19/126) in the KYONAL study*; they were predominantly mild and primarily affected the gastrointestinal system
- The majority (67.9%) of reactions appeared within the first 15 days of treatment and resolved with time
- During 12 months of follow-up, 6 patients required treatment discontinuation and study withdrawal due to adverse reactions**
- The safety profile of naloxegol in this study is consistent with that observed during the clinical development of the drug

Adverse reactions†	% (n)
Patients with any adverse reaction	15.1 (19)
Intensity (n=28)	
Mild	75.0 (21)
Moderate	17.9 (5)
Severe	7.1 (2)
Adverse reactions (n=28)	
Abdominal pain	46.4 (13)
Diarrhoea	21.4 (6)
Abdominal bloating	17.9 (5)
Nausea	10.7 (3)
Dysaesthesia	3.6 (1)

† Table created from data in publication

* Three patients were on concomitant laxatives.

** The adverse reactions were: abdominal pain (6), nausea (1), diarrhoea (2). The withdrawal due to adverse reactions occurred before Day 15 in 3 patients and between 15 and 30 days in 3 patients. Five patients were on 25 mg naloxegol and one patient was on the 12.5 mg dose.

1. Cobo Dols M, Beato Zambrano C, Cabezon-Gutierrez L, *et al*. *BMJ Supportive & Palliative Care* Epub ahead of print: March 2021. doi:10.1136/bmjspcare-2020-002816

KYONAL 12-month results: conclusions

- **Significant response to naloxegol** treatment was seen in **77.8%** (n=98) of **cancer patients with OIC at 12 months**[1]
- **Clinically and statistically significant improvements in OIC-related QoL** (assessed using PAC-QOL) were observed from 15 days after treatment initiation and **persisted during 12 months** of follow-up[1]
  - Largest improvement was observed in the **patient satisfaction subscale** of the PAC-QOL[1]
- **Clinically and statistically significant improvements** were also observed in **symptom-assessment scores** (PAC-SYM) from Day 15 to Month 12[1]
- **Statistically significant improvements** ($p<0.0001$) in **SBMs and stool consistency** from baseline at all study visits[1]
  - Cancer patients with OIC treated with naloxegol significantly increased spontaneous bowel movements (SBMs) per week from a mean of 2.3 to 4.2 on Day 15 and this improvement was maintained, with a mean of 4.5 SBMs per week at Month 12 ($p<0.0001$) [1]
- Naloxegol was shown to be **effective alone or in combination with laxatives**[1]*
- **Adverse reactions were observed in 15.1% of patients (19/126); most appeared in the first 15 days of treatment and resolved with time**[1]
  - Adverse reactions were mainly gastrointestinal, and **mostly mild (75%) to moderate (17.9%)**[1]
- Naloxegol 25mg once daily **does not interfere with opioid treatment for pain management in patients with OIC**[1,2]
  - **Analgesic response was maintained throughout the** 12-month follow-up period[1]
- These data provide the **first real-world evidence of long-term efficacy and safety of naloxegol treatment for OIC in patients with cancer**[1]

OIC, opioid-induced constipation; QoL, quality of life; SBM, spontaneous bowel movement; PAC-QOL, Patient Assessment of Constipation Quality of Life Questionnaire; PAC-SYM, Patient Assessment of Constipation Symptoms

* When MOVENTIG therapy is initiated, it is recommended that all currently used maintenance laxative therapy should be halted, until clinical effect of MOVENTIG is determined[2]

1. Cobo Dols M, Beato Zambrano C, Cabezon-Gutierrez L, *et al*. *BMJ Supportive & Palliative Care* Epub ahead of print: March 2021. doi:10.1136/bmjspcare-2020-002816
2. **MOVENTIG** Summary of Product Characteristics.

Thank you.

Grünenthal
Meds

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
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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 May 2019
   http://www.oecd.org/health/addressing-problematic-opioid-use-in-oecd-countries-a18286f0-en.htm

KKI/INT/KKI/0803 June 2023