9 November 2023
EMA/554500/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Moventig

International non-proprietary name: naloxegol

Procedure No. EMEA/H/C/002810/II/0039

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Kyowa Kirin Holdings B.V. submitted to the European Medicines Agency on 12 October 2022 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Update of sections 4.1, 4.2, 4.4, 4.8, 5.1, and 5.2 of the SmPC in order to update information regarding the use of naloxegol in OIC patients with cancer-related pain based on real-world data from non-interventional studies (NACASY, KYONAL, and MOVE studies), post-marketing data, and literature. The Package Leaflet is updated accordingly. The RMP version 8 has also been submitted. In addition, the MAH took the opportunity to implement editorial changes to the SmPC.

The variation requested amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The MAH did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Christophe Focke Co-Rapporteur: Ewa Balkowiec Iskra

Status of this report and steps taken for the assessment				
Current step[1]	**Description**	**Planned date**	**Actual Date**	**Need for discussion[2]**
☐	Start of procedure	27 Jan 2023	27 Jan 2023	☐
☐	CHMP Rapporteur Assessment Report	24 Mar 2023	27 Mar 2023	☐
☐	CHMP Co-Rapporteur Critique	04 Apr 2023	27 Mar 2023	☐
☐	PRAC Rapporteur Assessment Report	31 Mar 2023	31 Mar 2023	☐
☐	PRAC members comments	04 Apr 2023	05 Apr 2023	☐
☐	Updated PRAC Rapporteur Assessment Report	05 Apr 2023	05 Apr 2023	☐
☐	PRAC endorsed relevant sections of the assessment report[3]	14 Apr 2023	14 Apr 2023	☐
☐	CHMP members comments	17 Apr 2023	17 Apr 2023	☐
☐	Updated CHMP Rapporteur(s) (Joint) Assessment Report	20 Apr 2023	20 Apr 2023	☐
☐	RSI	26 Apr 2023	26 Apr 2023	☐
☐	Submission	11 Sept 2023		☐
☐	CHMP and PRAC Rapporteur Assessment Report	10 Oct 2023	11 Oct 2023	☐
☐	PRAC members comments	18 Oct 2023	n/a	☐
☐	Updated PRAC Rapporteur Assessment Report	19 Oct 2023	n/a	☐
☐	PRAC endorsed relevant sections of the assessment report[3]	26 Oct 2023	26 Oct 2023	☐
☐	CHMP members comments	27 Oct 2023	27 Oct 2023	☐
☐	Updated CHMP Rapporteur(s) (Joint) Assessment Report	31 Oct 2023	31 Oct 2023	☐
☒	Opinion	09 Nov 2023	09 Nov 2023	☐

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

Opioid-induced bowel dysfunction is a complication of opioid therapy, in which constipation is the most common and problematic symptom (Farmer et al., 2019).

State the claimed the therapeutic indication

Moventig is indicated for the treatment of opioid-induced constipation (OIC) in adult patients who have previously been treated with a laxative.

Aetiology and pathogenesis

Opioids are a class of potent analgesics, and their use has increased markedly in recent years. Opioids are associated with a variety of bothersome side effects such as sedation, lethargy and pruritus, notwithstanding the considerable risk of addiction. Opioids also adversely impact the sensorimotor function of the gastrointestinal tract, via the action of exogenous opioid agonists, on the enteric nervous system. Such adverse effects limit dose escalation and can necessitate a switch in opioids or even cessation of therapy. The term opioid-induced bowel dysfunction (OIBD) encompasses a spectrum of symptoms including nausea, vomiting, bloating, gastro-oesophageal reflux-related symptoms and constipation. Opioid-induced constipation (OIC) is the most common subtype of OIBD that occurs in 51–87% of patients receiving opioids for cancer and between 41–57% patients receiving opioids for chronic non-cancer pain (Farmer et al., 2019).

Clinical presentation

The term opioid-induced bowel dysfunction (OIBD) encompasses a spectrum of symptoms including nausea, vomiting, bloating, gastro-oesophageal reflux-related symptoms and constipation. Opioid-induced constipation (OIC) is the most common subtype of OIBD that occurs in 51–87% of patients receiving opioids for cancer and between 41–57% patients receiving opioids for chronic non-cancer pain (Farmer et al., 2019).

Management

The pathophysiology of opioid-induced constipation is multi-faceted and 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. 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 (Farmer et al., 2019).

Standard laxatives, such as osmotic agents (macrogol) and stimulants (bisacodyl, picosulphate and senna) are good first-line choices in the management of OIC (Farmer et al., 2019).

Opioid-receptor antagonists can alleviate the adverse effects of opioids on GI functions, but their central analgesic effects may also be antagonised if they cross the blood-brain barrier. The most readily well-known example is naloxone, commonly used as an intravenous reversal agent in the context of opioid over-dosing. Agents that block mu-opioid receptors in the GI tract, but do not enter the central nervous system (CNS), are expected to treat OIBD without diminishing central analgesic actions. Several opioid antagonists with local action within the gut or (outside the CNS) peripherally-acting mu-opioid receptor antagonists (PAMORAs) have become available such as methylnaltrexone, naldemedine and naloxegol (Farmer et al., 2019).

2.1.2. About the product

Moventig is a medicine used in adults to treat constipation caused by pain relief medicines called opioids. It is used in patients in whom treatment with laxatives has failed.

The active substance in Moventig, naloxegol, is a peripheral mu-opioid-receptor antagonist. This means that it attaches to a specific type of opioid receptor called the 'mu-opioid receptor' and blocks opioids from binding to these receptors. Naloxegol is derived from naloxone, a well-known substance that is used to block the action of opioids. Naloxegol is less able to enter the brain than naloxone, meaning that it can block the mu-opioid receptors in the gut but less in the brain. By blocking receptors in the gut, Moventig reduces the constipation due to opioids, but does not interfere with their pain relief effects.

Moventig (naloxegol) was approved by the EMA in 2014 for the treatment of opioid-induced constipation (OIC) in adult patients who have had an inadequate response to laxative(s). It was recommended to halt other maintenance laxative therapy at initiation until the clinical effect of naloxegol was determined (SmPC 4.2) and in addition, experience in cancer pain related OIC was minimal (as described in 4.4 of the SmPC).

In several publications, the efficacy and safety of naloxegol with or without standard laxatives in cancer pain related OIC is discussed, and the MAH presents data from these studies (Cobo Dols, Beato Zambrano, Cabezón-Gutiérrez, et al., 2021; Cobo Dols, Beato Zambrano, Cabezón Gutiérrez, et al., 2021; Davies et al., 2022; Lemaire et al., 2021).

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

The applicant did not seek scientific advice at the CHMP. The EMA Guideline on the evaluation of medicinal products for the treatment of chronic constipation (including opioid induced constipation) and for bowel cleansing is applicable for the assessment of this procedure.

2.1.4. General comments on compliance with GLP, GCP

N/A

2.2. Non-clinical aspects

No new clinical data have been submitted in this application, which is considered acceptable.

An Environmental Risk Assessment (ERA) had already been undertaken for naloxegol (previously known as NKTR-118) in accordance with EMA Guidance (CHMP 2006) at initial Marketing Authorisation. This ERA utilized the default values for the Default Predicted Environmental Concentration (PEC) Calculation, which remains unchanged. As the applicant withdrew the claim to extend the indication (please also refer to the chapter "discussion on clinical efficacy) there will be no increase in environmental exposure further to the use of naloxegol.

2.3. Clinical aspects

2.3.1. Introduction

In support of the changes in section 4.1, no (new) clinical data were submitted by the applicant. Instead, the MAH provided argumentation that the new indication may better reflect the class recommendation for PAMORAs (De Giorgio, et al., 2021) and the way Moventig is used in clinical practice.

In support of the proposed changes in section 4.2 and 4.4, the applicant submitted a clinical overview in which real world data, i.e. observational studies (Kyonal, NACASY and MovE), are briefly discussed through the citing of the content of publications. No results were submitted that were generated in controlled clinical studies and, in a recent Cochrane review on mu-opioid antagonists for opioid-induced bowel dysfunction in people with cancer and people receiving palliative care, it was reported that at present no clinical trials with naloxegol have published results (Candy, Jones, Vickerstaff, Larkin, & Stone, 2022). The SmPC changes for which the MAH seeks approval are i) approval of the concomitant use with standard laxatives and ii) deletion of the statement that experience in OIC patients with cancer related pain is limited. Furthermore, editorial edits are proposed to other parts of the SmPC.

In response to the first list of outstanding issues, the MAH pooled the data from three observational studies, Kyonal, NACASY and MovE, to allow a more consistent analysis of 4 week efficacy and safety data. Real world evidence from these studies was requested for inclusion in 5.1. of the SmPC.

The proposed changes to *4.1, 4.2 and 4.4* of the SmPC are reflected in the below table.

Table 1 Proposed Changes to 4.1, 4.2 and 4.4. of the SmPC

Current SmPC	Proposed SmPC
Section 4.1 Moventig is indicated for the treatment of opioid-induced constipation (OIC) in adult patients who have had an inadequate response to laxative(s). For definition of inadequate response to laxative(s), see section 5.1	Moventig is indicated for the treatment of opioid-induced constipation (OIC) in adult patients who have previously been treated with a laxative(s).
Section 4.2 When Naloxegol therapy is initiated, it is recommended that all currently used maintenance laxative therapy should be halted, until clinical effect of naloxegol is determined. No dose adjustment is required for patients with cancer-related pain (see sections 4.3 and 4.4).	Moventig may be used with or without laxative(s). Moventig treatment should be withdrawn when systemic opioid therapy is stopped. No dose adjustment is required for patients with cancer-related pain (see sections 4.3).
Section 4.4 Cancer-related pain There is limited clinical experience with the use of naloxegol in OIC patients with cancer-related pain. Therefore, caution should be used when prescribing naloxegol to such patients (see section 4.3)	Caution removed and RWE data included in Section 5.1 SmPC

2.4. Clinical efficacy

2.4.1. Main study(ies)

KYONAL study

A prospective, observational study of a cohort of patients with cancer and with OIC exhibiting an inadequate response to laxatives and treated with naloxegol.

The primary endpoint was the assessment of constipation-related quality of life in the patients receiving naloxegol, using the Patient Assessment of Constipation Quality of Life Questionnaire (PAC-QOL), in its validated Spanish version. Changes in the total or subscale scores of ≥0.5 points were considered clinically relevant. A higher PAC-QOL score means poorer quality of life.

The secondary endpoints included evaluation of the efficacy of naloxegol in treating OIC over follow-up, defined as the proportion of responders: patients with three or more bowel movements a week, and one or more bowel movements a week additional to the number of bowel movements at baseline.

As secondary efficacy endpoint, constipation symptoms were evaluated using the Patient Assessment of Constipation Symptoms (PAC-SYM) in its validated Spanish version, referred to the last 2 weeks.

The safety of naloxegol treatment was assessed based on the adverse reactions described during patient follow-up.

Results of the three month follow-up (Cobo Dols, Beato Zambrano, Cabezón Gutiérrez, et al., 2021) and 12 month follow-up (Cobo Dols, Beato Zambrano, Cabezón-Gutiérrez, et al., 2021) were published and discussed by the MAH, and included in section 5.1 of the SmPC.

Results

Cobo Dols 2021a: 3 month follow up

A total of 126 patients (58.2% males) with a mean age of 61.3 years (range 34–89) were included. 95 patients completed the 3 months of follow-up. 3 patients discontinued the study due to physician decision; 10 discontinued the study due to patient decision; 1 patient was lost to follow-up; and 17 patients had died because of their oncological disease.

During the study, 63.2% of the patients (n=43) received concomitant treatment with laxatives. At baseline, 63.2% of the patients (n=74) were receiving chemotherapy and 85.2% (n=98) were receiving treatment with other drugs that could cause constipation.

A total of 82.5% of the patients (n=85) responded to treatment with naloxegol after 15 days, 83.2% after 1 month (n=79) and 87.7% after 3 months (n=64). Seventeen patients (13.5%) experienced some adverse reaction (AR) to naloxegol, mostly of a GI nature.

Significant improvement of OIC-related QOL was observed as early as 15 days (in 63% patients) after the start of the treatment and persisted during the 3 months (in 75.4% patients) to follow-up. Evolution of the mean PAC-QOL score is shown in Figure 1. A statistically significant increase in the mean number of days a week with complete spontaneous bowel movements from baseline ($p<0.0001$) was observed over all the study visits (Figure 2).Clinical symptoms efficacy assessed by the PAC-SYM questionnaire also yielded statistically significant findings. The proportion of patients with clinically relevant improvement was 64.5% after 15 days and 84.1% after 3 months.

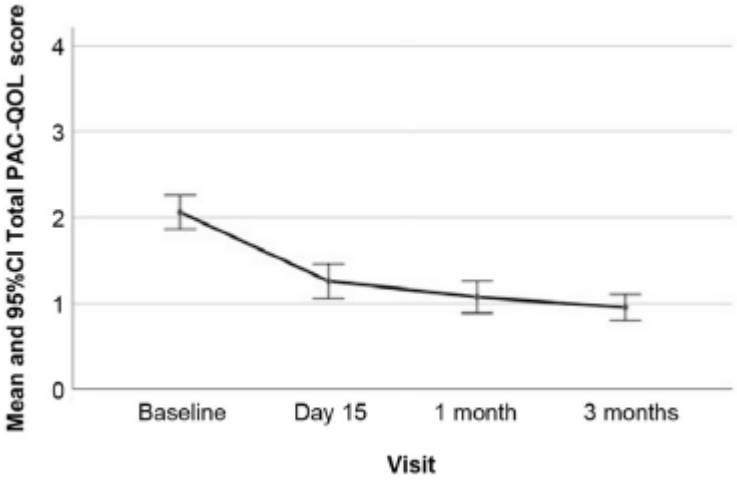


Figure 1 Evolution of total Patient Assessment of Constipation Quality of Life Questionnaire (PAC-QOL) score from baseline to 3 months of follow-up ($p<0.0001$).

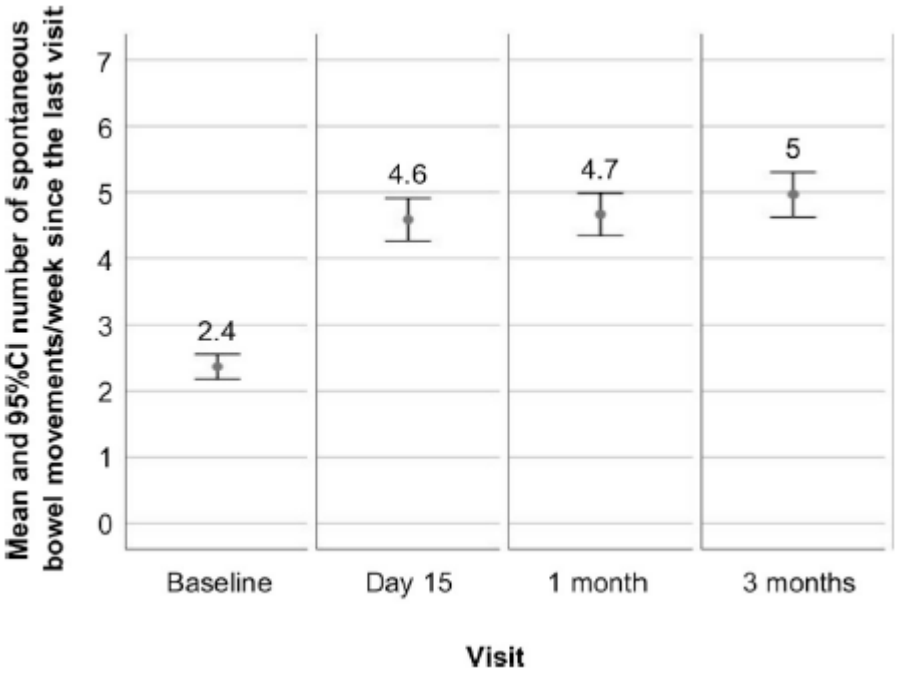


Figure 2 Mean number complete spontaneous bowel movements per week.

The authors concluded that naloxegol as treatment for OIC in patients with cancer with an inadequate response to laxatives was more effective than expected.

This study provides support for the efficacy and safety of naloxegol in OIC patients with cancer-related pain, including patients taking concomitant laxatives.

Cobo Dols 2021b: 12 month follow up

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 scores and all their dimensions improved from baseline ($p<0.0001$) and between all the subsequent visits. At 12 months, 77.8% of the patients were responders to naloxegol treatment. The percentage of patients with clinically relevant improvement in the total PAC-QOL score was 50.8% after 15 days, 60.3% after 1 month, 61.9% after 3 months, 57.1% at 6 months, and 58.7% at 12 months. Additionally, the proportion of patients with clinically relevant improvement in the total PAC-SYM scores was 54.8% after 15 days, 63.5% after 1 month, 64.3% after 3 months, 64.3% at month 6, and 65.9% at month 12. At 12 months, 77.8% of patients responded to naloxegol treatment. For the global QOL, there were no significant changes from baseline to 6 and 12 months.

Concomitant laxatives use was reported in 61 (48.4%) of the patients. 9 patients (7.1%) needed rescue laxatives: lactulose (39.4%), macrogol (26.8%) and bisacodyl (9.9%). No significant response rate differences were demonstrated by dose and/or concomitant laxative use. However, for patients treated with doses of 25 mg of naloxegol, a slight but not significantly better response rate for patients on concomitant laxatives was observed (Figure 3). The authors speculate that this could be attributable to concurrent non-OIC constipation in the patients who had some prior constipation before initiation of treatment with opioids (27.8%), and patients receiving concomitant treatment with other drugs that could induce non-OIC constipation (84.9%). In both of these cases additional laxatives with other mechanisms of action would be expected to be beneficial.

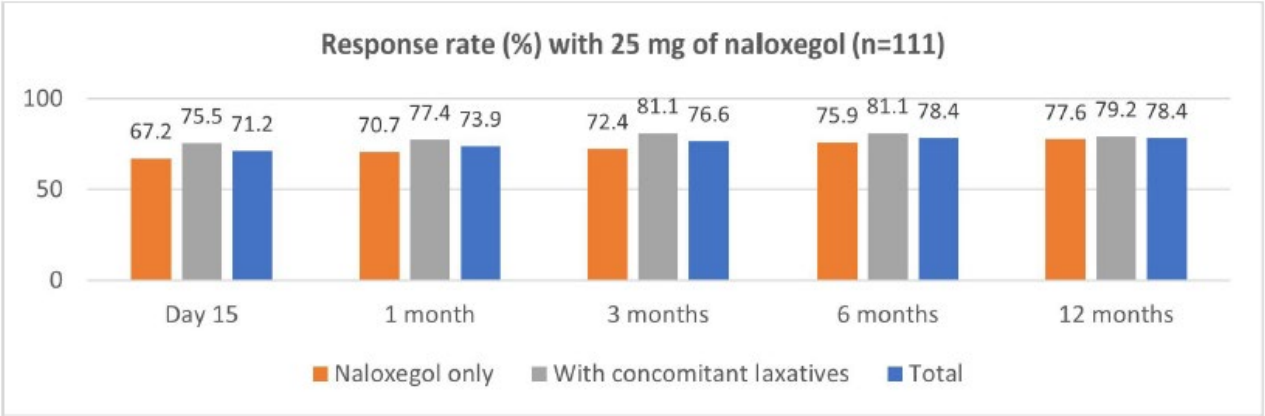


Figure 3 Response rate to naloxegol according to use of concomitant laxative

A total of 28 ARs, mainly GI were observed in 15.1% of the patients (19/126), being 75% (21) mild, 17.9% (5) moderate and 7.1% (2) severe. Most ARs (67.9%) appeared in the first 15 days of treatment. All ARs were resolved. Six patients were withdrawn from the study due to ARs: abdominal pain (6), nausea (1), diarrhoea (2).

3 patients with ARs were on concomitant treatment with other laxatives. In 4 patients naloxegol was temporarily suspended, in 1 patient the naloxegol dose was reduced and in 17 patients no action was taken. During the study, 53 patients died from causes related to their malignant disease with no differences from the expected cancer-related incidence.

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 patients with cancer related pain.

NACASY study

The NAloxegol CAncer StudY (NACASY) was a prospective, observational, single-arm, open-label, multinational European study aimed to evaluate the 4-week safety and efficacy of naloxegol in a real-world setting in patients with cancer pain diagnosed with OIC.

The primary safety endpoint was the incidence of adverse events (AEs) leading to study discontinuation.

The primary efficacy endpoint was the response rate during the 4 weeks of treatment. Response rate was defined as the proportion of participants reporting ≥3 BM (without the use of rescue laxative treatment in the previous 24 h) per week and an increase of ≥1 BM over baseline.

Results of the study were published (Davies et al., 2022) and presented in the clinical overview.

Results

The study recruited 170 patients from 26 European centres, who received at least 1 dose of naloxegol (i.e., safety population), and the primary efficacy endpoint was the response rate during the treatment time. There were 2 efficacy populations studied: population 1 – subjects who had completed 4 weeks of treatment and 28 days of the diary, and population 2 – subjects who had completed at least 21 days of the diary and were not study discontinuous. 183 patients were recruited for this study, and 170 were analysed (n=170 for the safety analysis, n=143 for the efficacy of which n=76 were in population 1, and n=98 were in population 2).

At baseline, 104 of 143 (72.7%) subjects were receiving conventional laxatives, and the corresponding proportions at visits 2 and 3 were 105/140 (75%) and 43/118 (36.4%), respectively. Osmotic and stimulant laxatives were the most frequently used at every study visit (data not shown). Furthermore, the most frequently used baseline laxatives were: osmotic laxatives (79.8%), stimulant laxatives (30.8%), stool softeners (11.58%), and other (18.3%, enema being the most common, with 9.6%). The study results were not presented separately for subgroups defined by laxative use.

Overall, 89 of 170 study subjects (52.4%) reported at least 1 AE, and 38 (22.4%) were recorded as serious AEs. There were 21 deaths in the study with 1 of these (intestinal perforation) having a possible causal relationship with naloxegol. Treatment-related AEs (n=23, 13.5%) were mainly GI (Table 2), the most frequently reported being abdominal pain (n = 14, 8.2%) and diarrhoea (n = 5, 2.9%). Except for a case of intestinal perforation that was categorized as grade 5, the remaining evaluable AEs were graded 1-3. There were 2 (1.2%) treatment-related AEs that were considered serious: a case of grade 5 intestinal perforation and a case of grade 2 diarrhoea. The intestinal perforation occurred in a 68-year-old male, diagnosed with advanced pancreatic cancer, and with a medical history of gastric bypass surgery. Shortly after initiating treatment with 25 mg of naloxegol, the patient experienced rapid deterioration of the general state, showed signs of peritonitis, sepsis and multiorgan failure, and finally died. An autopsy was not performed, and the event was categorized by the investigator as probable intestinal perforation.

Out of 170 patients, 20 (11.8%, 95% CI [6.9-16.6]) discontinued the study due to AE, and, of them, 12 (7.1%, [3.2-10.9%]) were study discontinuations due to naloxegol-related AEs. These were mainly GI side effects, including 8 cases of abdominal pain, 2 cases of diarrhoea, and 1 due to the fatal intestinal perforation; the remaining patient discontinued the study due to fatigue.

From 76 patients who had completed both 4 weeks of treatment and 28 days of the diary, 55 patients (72.4%, [62.3-82.4%]) were regarded as responders (i.e., showed ≥3 bowel-movements per week and an increase of ≥1 bowel-movement over baseline) to naloxegol treatment. The PAC-QOL total score and all its subscales improved from baseline to 4 weeks of follow up.

The authors consider that the findings support and provide new evidence about the beneficial effect of naloxegol in terms of improvement of constipation and QOL in patients with cancer-related pain and OIC and show a safety profile consistent with previous pivotal and real-world studies. The study also supports continuing use of laxatives during the initiation of naloxegol treatment.

MovE study

The MovE study, reported by Lemaire et al. (Lemaire et al., 2021), was a non-interventional prospective, multicentre French real-world study, with a 4-week follow-up period investigating the effectiveness of naloxegol in patients with cancer pain suffering from OIC. This study, conducted in 24 French oncology and pain centres between 2018 and 2019, mainly aimed to assess in real-life conditions the efficacy and safety of naloxegol in cancer pain patients and the evolution of their QOL. Eligible patients were aged ≥ 18 years, treated with opioids for cancer pain, and started naloxegol for OIC with inadequate response to laxatives.

The primary efficacy criterion was the response rate to naloxegol at week 4 (defined as follows: ≥ 3 bowel movements during the 4th week, with or without combined laxatives during follow-up, and an increase of ≥ 1 bowel movement per week between inclusion and W4.) Additionally, the PAC-QOL was used to measure the evolution of QoL. The analysis of the primary efficacy criterion (response rate in patients with or without concomitant laxatives, based on the data reported by the physicians) was repeated in the subgroups of patients with and without laxatives during study follow-up and using data from the 28-day diaries completed by patients.

Results

A total of 124 patients were included, with 86 patients (69.4%) completing the study at week 4. The main reasons for early study termination included patient death, patient decision, and lost to follow-up. The patients' characteristics were: 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.

In the efficacy population, at week 4 (W4), 73.4% of patients had a clinically relevant change in QoL, which was a decrease in PAC-QOL score of ≥0.5 point. Additionally, amongst the analysed patients, most physicians and patients were satisfied with the treatment at week 4, with ratings of ≥5 observed in 81.4% and 72.4% of the cases, respectively.

The response to treatment at W4 (primary criterion) was reached by most of the 79 evaluable patients in the efficacy population (73.4%, 95% CI [63.7–83.2%]), irrespective of the use of laxatives during patient follow-up (76.7% [66.0–87.4%] and 63.2% [41.5–84.8%], respectively, with and without laxatives). The proportions of responder patients at the 4th week are graphically presented with their associated confidence intervals in Figure 4.

At least 1 AE was reported by 43 patients (32.8%), including 21 patients (16%) reporting at least 1 serious AE. AEs related to naloxegol were reported in 8% of patients (7% with GI events mainly diarrhoea; 1 serious diarrhoea). The safety profile was consistent with the known safety profile.

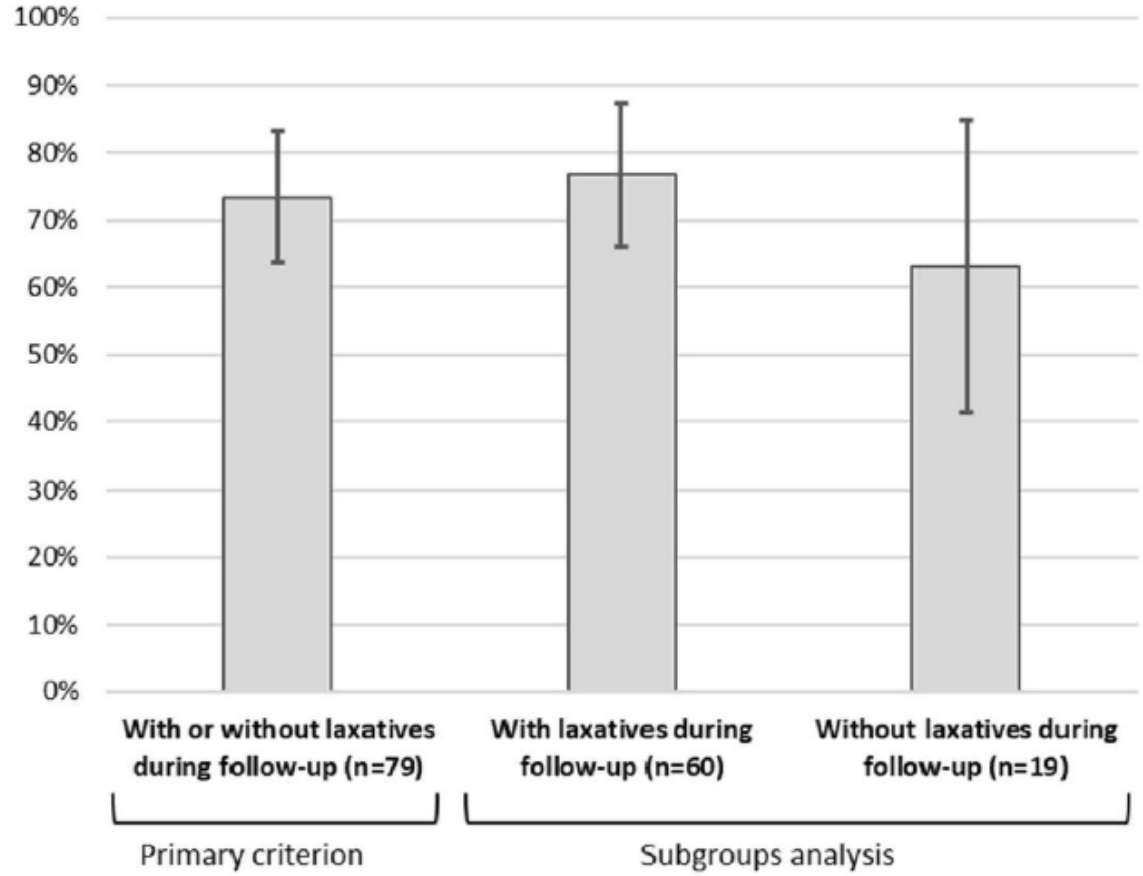


Figure 4 Response to naloxegol at week 4 in the MovE Study.

The 73% overall response rate to naloxegol at week 4 was higher than in previous clinical trials conducted in non-cancer patients, with no concomitant laxative use permitted (48.7% and 46.8% at week 12 in the KODIAC-04 and KODIAC-05 studies, respectively). Even if it is recommended in Europe

that all currently used maintenance laxative therapy should be halted when naloxegol therapy is initiated, in this real-world study, the majority of the patients received concomitant laxatives during follow-up. This therapeutic choice of physicians involved in the care of cancer patients may be explained by the multifactorial cause of the constipation that may require treatments with synergetic mechanisms of action. Recent real-world studies conducted in cancer patients with OIC also showed similar high response rates under naloxegol treatment. Finally, the high overall response rate to naloxegol is constant with available literature data in cancer patients with OIC. The differences in proportion could be explained by potential concomitant laxatives but also by other treatments taken by such cancer patients in a real-life setting (in particular in metastatic patients) as, in this study, the authors stated that most patients in both groups (with or without combined laxatives) also received treatments that could lead to constipation.

The authors concluded that in this real-world study, naloxegol was effective and well tolerated in cancer pain patients with OIC and that their quality of life improved under treatment. This study also supports the introduction of naloxegol in addition to existing conventional laxative treatments.

Analysis performed across trials (pooled analyses and meta-analysis)

Nalopool

In its response to the first round of outstanding issues, the applicant submitted an analysis of pooled data from the observational studies Kyonal, NACASY and MovE.

This pooling is most relevant for the expansion of the clinical safety experience with naloxegol in two conditions that were not investigated in the original naloxegol studies, i.e. use in cancer pain OIC patients and use concomitantly with standard laxatives.

The pooled data, which concerned a 4 week treatment period in which efficacy and safety of naloxegol was investigated in cancer pain OIC patients, confirmed the efficacy of naloxegol in treatment of OIC in cancer pain patients, either with or without concomitant laxatives.

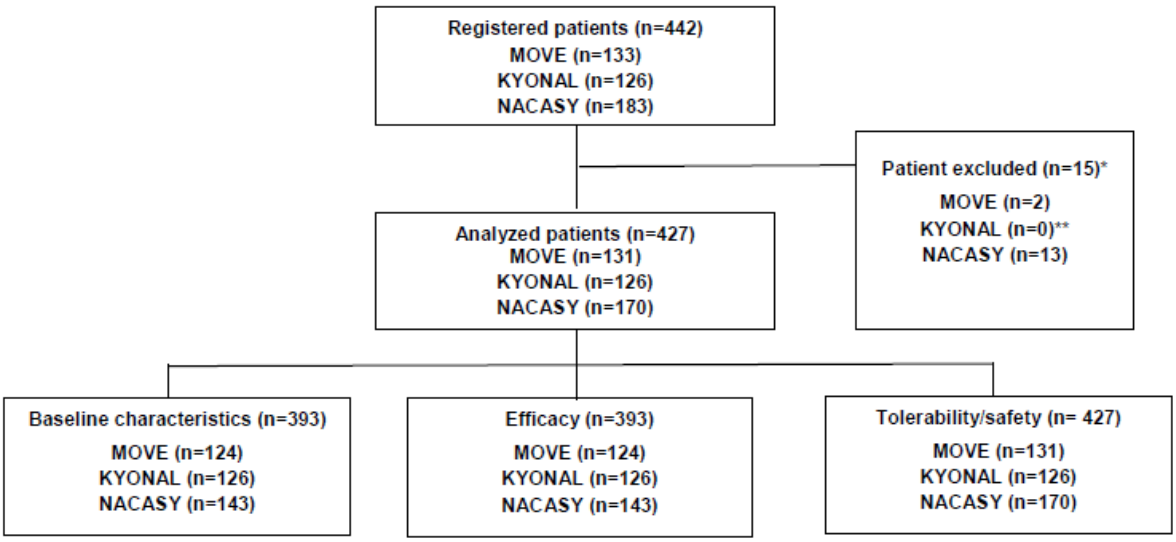
The Nalopool is a pooled database that combines clinical data from the first 4 week treatment period of 3 studies, the KYONAL, MOVE and NACASY studies, and comprises real-world data from 420 patients with cancer pain and OIC.

All three studies included adult patients with cancer pain requiring treatment with opioids and who experienced OIC. With slight differences across studies, OIC definitions were compatible with Rome IV criteria. All three studies use non-stringent exclusion criteria with slight differences among them.

Efficacy

Primary efficacy endpoints for the Nalopool study were SBM and PAC-QOL, investigated in the individual studies.

Figure 1: Disposition of subjects



The studies each contributed about one third of patients in the Nalopool. Mean and median age and BMI were comparable in between studies. The majority of patients was male in the Kyonal and Move studies, and female in the Nacasy study. 65% of patients had metastases indicating in general a population with advanced cancer was recruited. Fentanyl, oxycodone and morphine were mostly used, and about one third of patients had received more than one opioid. Median and mean time of opioid use were 8.9 weeks and 24.9 weeks indicating this opioid usage distribution was right skewed. Osmotic laxatives had been used by 90% of patients.

83% of patients initiated naloxegol treatment on a 25 mg dose, and 43% used concomitant laxatives (for the latter, no Kyonal study data were available). During the study, opioid product changes and opioid dose increases were noted, the latter in 16.1% of patients. 10% of patients discontinued naloxogel during the respective studies.

The efficacy assessment was performed for the efficacy population, N=393 (defined as all patients who meet all selection criteria, received at least 1 dose of study drug and have at least one post-baseline efficacy assessment).

Primary efficacy endpoint 1: Spontaneous bowel Movements (SBM)

Response has been defined with the following:

- SBM response: three or more SBM per week at visit week 4.

- SBM strict response: three or more bowel SBM with an increase of one or more SBM over baseline. In Nacasy study the increase of 1 SBM from baseline is assumed, when patients reach 3 SBM/week, due to study characteristics (All patients included in Nacasy study had less than 3 SMB at baseline, before naloxegol start date).

		STUDY							
		Kyonal		Move		Nacasy		Total	
		N	%	N	%	N	%	N	%
SBM response rate (week 4)	No response	20	15,9	16	19,8	38	34,9	74	23,4
	Response	106	84,1	65	80,2	71	65,1	242	76,6
	Total	126	100,0	81	100,0	109	100,0	316	100,0
SBM strict response rate (week 4)	No response	32	25,4	21	26,6	38	34,9	91	29,0
	Response	94	74,6	58	73,4	71	65,1	223	71,0
	Total	126	100,0	79	100,0	109	100,0	314	100,0

Primary efficacy endpoint 2: Quality of life – PAC-QOL

PAC-QOL Quality of life response has been defined as improvement of at least 0.5 points in the PAC-QoL total score (reduction of 0.5 points). 60% of the patient population of the Nalopool population demonstrated a clinically relevant response at week 4 of treatment. The PAC-QOL score was shown to be statistically different between week 4 and baseline for all subscales and for the global PAC-QOL score.

		STUDY							
		Kyonal		Move		Nacasy		Total	
		N	%	N	%	N	%	N	%
Quality of life response at week 4	QoL no response	44	38,9	31	41,3	45	40,5	120	40,1
	QoL response	69	61,1	44	58,7	66	59,5	179	59,9
	Total	113	100,0	75	100,0	111	100,0	299	100,0

Secondary efficacy endpoint: Impact on constipation symptoms

PAC-SYM

Constipation symptoms were measured using the Patient Assessment of Constipation Symptoms (PAC-SYM) scale in the KYONAL and MOVE studies (The PAC-SYM score was not evaluated in the Nacasy study). A reduction was seen in all dimensions of the PAC-SYM and statistically significant differences (all p≤0.001 using T-Student test for paired samples) were found between baseline and week 4 in all subscales and global score.

		PAC-SYM: Total score change from baseline (baseline - week 4)							
		N	Mean	Standard deviation	Minimum	Q1	Median (Q2)	Q3	Maximum
STUDY	Kyonal	115	,8	,8	-1,2	,2	,8	1,3	2,9
	Move	75	,8	,7	-1,3	,3	,8	1,3	2,1
	Total	190	,8	,8	-1,3	,3	,8	1,3	2,9

PAC-SYM response has been defined as improvement of at least 0.5 points in the PAC-SYM scores (reduction of 0.5 points).

		STUDY					
		Kyonal		Move		Total	
		N	%	N	%	N	%
PAC-SYM response	PAC-SYM no response	36	31,3	23	30,7	59	31,1
	PAC-SYM response	79	68,7	52	69,3	131	68,9
	Total	115	100,0	75	100,0	190	100,0

Bowel Function Index

The Bowel Function Index (BFI) was assessed in the MOVE and NACASY studies (BFI was not evaluated in the Kyonal study.). A reduction was seen in all dimensions of the BFI. Statistically significant differences (all p<0.001 using T-Student test for paired samples) were found between baseline and week 4 in all subscales and global score.

BFI: Total score change from baseline (baseline - week 4)									
		N	Mean	Standard deviation	Minimum	Q1	Median (Q2)	Q3	Maximum
STUDY	Move	79	30,9	29,9	-63,3	10,0	30,0	50,0	100,0
	Nacasy	116	28,1	31,5	-33,3	5,0	23,3	48,3	100,0
	Total	195	29,2	30,8	-63,3	6,7	26,7	50,0	100,0

BFI response was defined as improvement of at least 12 points in the BFI total score (reduction of 12 points). The percentage of BFI responders was 73.4% in the MOVE study and 64.7% in the NACASY study, giving an overall response rate of 68.2%.

		STUDY					
		Move		Nacasy		Total	
		N	%	N	%	N	%
BFI response	BFI no response	21	26,6	41	35,3	62	31,8
	BFI response	58	73,4	75	64,7	133	68,2
	Total	79	100,0	116	100,0	195	100,0

Concomitant use of laxatives

As described under Baseline Characteristics, all evaluable subjects had received at least 4 weeks of prior laxative treatment. Concomitant use of laxatives was reported by 114 patients (42.7%).

Additional Nalopool analyses could not detect any significant influence of concomitant laxative use on the efficacy of naloxagol. There was a trend to higher response rate without concomitant laxative use (p=0.053) which seems contradictory at first sight but which likely reflects the increased use of concomitant laxatives by patients who don't initially respond to naloxegol alone, or who have additional constipation of a separate non-OIC etiology.

2.4.2. Discussion on clinical efficacy

No clinical data were submitted in support of the proposed change in therapeutic indication.

KYONAL study

At first sight, the presented data suggest that the use of naloxegol in the treatment of cancer pain related OIC is efficacious and safe, both at 3 months and 12 months of follow up, and both with and without the concomitant use of standard laxatives. However, a detailed analysis of the methodology and the results is not possible due to the nature of these data (scientific publication) and the limited amount of information submitted and discussed by the MAH. Some crucial study details are lacking in the clinical overview presented by the MAH.

Furthermore, serious concerns on the analysis of the original data remain. For the final intention-to-treat analysis adjusted for missing data in the efficacy variables the last observation carried forward (LOCF) method was used. This approach is considered not acceptable because of the high number of dropouts in the study (29 of 126 patients were still included after 1 year) and because it cannot simply be assumed that a (non)response would have been preserved over time in the individual patient.

Stating that a PAC-QOL score of 58.7% (n=74) is observed at month 12 knowing that only 29 patients are still enrolled in the study at that time point, is not credible nor scientifically justified.

NACASY study

The data presented suggest that the use of naloxegol in the treatment cancer pain related OIC is efficacious and safe at four weeks of treatment, both with and without the concomitant use of standard laxatives. The primary efficacy endpoint (response rate based on bowel movement) was evaluated at week 4. A four week treatment period to assess efficacy and safety is considered sufficient in the OIC setting in patients with malignancy-related pain.

MovE study

The response to treatment at W4 (primary criterion) was reached by most of the 79 evaluable patients in the efficacy population (73.4%, 95% CI [63.7–83.2%]), irrespective of the use of laxatives during patient follow-up (76.7% [66.0–87.4%] and 63.2% [41.5–84.8%], respectively, with and without laxatives). The 73% overall response rate to naloxegol at week 4 was higher than in previous clinical trials conducted in non-cancer patients, with no concomitant laxative use permitted (48.7% and 46.8% at week 12 in the KODIAC-04 and KODIAC-05 studies, respectively). In this real-world study, the majority of the patients received concomitant laxatives during follow-up.

The MovE study data have been pooled by the MAH with Kyonal and NACASY study data to further establish efficacy and safety in cancer pain patients suffering from OIC with or without concomitant laxative use and expand clinical experience in these patients.

Cancer-pain OIC patients were not included in the pivotal phase 3 naloxegol studies. Although the clinical efficacy response is not considered to be different in cancer pain patient vs non-cancer pain patients, the following warning was included in the Moventig SmPC in section 4.4 at initial marketing authorisation: *There is limited clinical experience with the use of naloxegol in OIC patients with cancer-related pain. Therefore, caution should be used when prescribing naloxegol to such patients.* The MAH now presents additional data in support of the safe use of the product in cancer pain OIC patients to expand the clinical experience in these patients. Naloxegol use is contraindicated in some malignant conditions, but they are not the scope of this variation, and this contraindication remains.

In addition, no concomitant laxatives were used in the clinical studies in support of the naloxegol indication. The SmPC currently states that when naloxegol therapy is initiated, it is recommended that all currently used maintenance laxative therapy should be halted, until clinical effect of naloxegol is determined. The concomitant use with standard laxatives is not explicitly forbidden in the SmPC. The MAH now presents additional data in support of the safe use of naloxegol together with standard laxatives, in cancer pain OIC patients. Since the original approval of Moventig, the EMA has issued a guideline (Guideline on the evaluation of medicinal products for the treatment of chronic constipation (including opioid induced constipation) and for bowel cleansing, EMA/CHMP/336243/2013) which supports such add-on therapy approach in cancer pain OIC patients.

Observational study data are presented to substantiate the efficay and safety of naloxegol in cancer OIC patients that cannot be sufficiently treated with standard laxatives. In these studies, naloxegol was used with and without standard laxatives. The study data from three studies have been pooled for analysis in the Nalopool database.

Nalopool database

In the Nalopool database, data from the first 4 weeks of treatment were analysed. This is in line with the EMA guideline which states that in case an efficacy study is conducted in cancer pain OIC patients, the randomised treatment period may need to be shortened. However, it is considered that usually, at least a 4-week period may be needed to adequately assess efficacy and safety. In addition, the

guideline states that the withdrawal of the "usual" laxative medication may be skipped when investigating OIC in patients with underlying malignant conditions. In this case, an "add-on- setting" can be investigated. Of note, the EMA guideline was developed for prospective, clinical studies, the studies included in the Nalopool database were observational.

The display of the primary efficacy results is considered acceptable. The concerned guideline states that "In a situation when the conduct of efficacy study(ies) is considered necessary in OIC, it is generally expected that recruitment may turn out to be difficult in cancer pain patients. Therefore, it is considered acceptable to base the primary evaluation of efficacy on a numerical scale, in order to avoid the reduction of power with the construction of responder analyses." Here, a responder analysis however is presented.

The results for the SBM response and SBM strict response are fairly comparable, showing 77% and 71% response rate, respectively. The CHMP considers these results as clinically relevant because of the magnitude of effect that is shown. For comparison, in the pivotal phase III studies in non-cancer pain OIC, the placebo effect for a (different) SBM-based response rate was about 30%.

The PAC-QOL results are in line with the SBM data and further support the efficay of naloxegol in this patient population. A clinically relevant PAC-QOL response was observed in 60% of patients.

The PAC-SYM results are in line with the SBM data and further support the efficay of naloxegol in this patient population. A clinically relevant PAC-SYM response was observed in 69% of the patients in which this outcome was measured.

The BFI results are in line with the SBM data and further support the efficay of naloxegol in this patient population. A clinically relevant BFI response was observed in 68% of the patients in which this outcome was measured.

In conclusion, the efficacy analyses of the pooled data from three observational studies show very consistent responses over the individual endpoints, supporting the use of naloxegol in the treatment of OIC in cancer pain patients. Accordingly the deletion of the precautionary statement on the use in OIC patients with cancer related pain from chapter 4.4 of the SmPC is supported. The existing contraindication in patients with heightened risk of GI perforation remains.

Concomitant laxative use was not allowed in the pivotal phase 3 trials for Moventig in the treatment of OIC non-cancer pain patients but is accepted in clinical practice in cancer pain OIC patients. As is stated in the guideline, in cancer pain OIC patients the mechanism for constipation may be from other causes related to the malignancy and not just be from opioids. The guideline supports that withdrawal of the "usual" laxative medication is skipped and an "add-on- setting" is investigated. In the current Moventig SmPC, the concomitant use with standard laxatives is not explicitly forbidden, but recommended to be halted until the effect of naloxegol is established.

The presented data do not raise concerns with regard to the efficacy of naloxegol in patients concomitantly taking laxatives and can be considered supportive amending 4.2 of the SmPC in order to allow the concomitant use of laxatives without stopping the maintenance laxative first. As the mechanism of action of Naloxegol is the same in cancer and non-cancer pain OIC patients the observations are considered to apply for cancer pain and non-cancer pain OIC patients.

The applicant further applies for implementing data from studies Kyonal, NACASY and MovE into 5.1. of the SmPC.

However the CHMP did not agree with including this observational data due to quality concerns and suitability for the SmPC. The methodological and statistical concerns, such as the aspect of "(lack of) predefinition" and data-driven analysis, had not been solved convincingly, and bias (primarily confounding by indication) cannot be excluded. Taking into consideration the SmPC guideline stating

that "It may be appropriate to provide limited information, relevant to the prescriber, such as the main results (statistically compelling and clinically relevant) regarding pre-specified end points or clinical outcomes in the major trials and giving the main characteristics of the patient population. Such information on clinical trials should be concise, clear, relevant and balanced, and should summarize evidence from relevant studies supporting the indication." The CHMP, whilst agreeing on the supporting evidence for the changes in 4.2 and 4.4. as outlined in this report disagreed to include this RWE into 5.1 of the SmPC. The MAH agreed with this approach.

The MAH submitted a variation application under category C.1.6.a of the variation classification Guideline with the scope to "Update of sections 4.1, 4.2, 4.4, 4.8, 5.1, and 5.2 of the SmPC in order to update information regarding the use of naloxegol in OIC patients with cancer-related pain based on real-world data from non-interventional studies (NACASY, KYONAL, and MOVE studies), post-marketing data, and literature. The Package Leaflet is updated accordingly. The RMP version 8 has also been submitted. In addition, the MAH took the opportunity to implement editorial changes to the SmPC.

The variation requested amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP)."

Based on the assessment of the data contained in the application, the CHMP is of the view that the following changes to the MA should be introduced ""Update of sections 4.2 and 4.4 of the SmPC based on real-world data from non-interventional studies (NACASY, KYONAL, and MOVE studies), post-marketing data, and literature on the use of naloxegol in OIC patients with cancer-related pain. The Package Leaflet is updated accordingly.

The RMP version 8.2 has also been submitted. In addition, the MAH took the opportunity to implement editorial changes to the SmPC" These changes fall under category C.1.4 of the variation classification Guideline.

During the procedure, the MAH updated the product information accordingly.

2.4.3. Conclusions on the clinical efficacy

Data from the individual observational studies and the analysis of pooled data confirmed the efficacy of naloxegol in the treatment of OIC in cancer pain patients, with or without concomitant laxatives. Since the bulk of efficacy data for naloxegol had been generated in controlled clinical trials, and a similar effect was expected in cancer pain patients, the expansion of clinical experience in cancer pain patients with data from observational studies is acceptable, since they only serve to further support an already granted indication. Accordingly, the applied changes to 4.2 and 4.4. are considered acceptable.

In accordance with the SmPC guideline the addition of data from RWE studies Kyonal, NACASY and MovE into 5.1 of the SmPC was not agreed. This claim was withdrawn by the applicant during the procedure.

The MAH proposed to change the approved therapeutic indication as follows: Moventig is indicated for the treatment of opioid-induced constipation (OIC) in adult patients who have previously been treated with a laxative, removing the restriction of the indication to laxative inadequate responders. However, no new data were submitted in support of the proposed change in therapeutic indication and the extension the indication claim was only supported based on the argument that the new indication may better reflect the class recommendation for PAMORAs (De Giorgio, et al., 2021) and the way Moventig is used in clinical practice.

However, the data availible on Moventig and assessed at the time of the initial marketing authorisation only supported a positive B/R in an OIC population with a documented inadequate response to

laxatives, and not in the population where such inadequate response was not documented, even though many of the latter patients had used a standard laxative before at some point. Results from the observational studies MovE, NACASY and KYONAL were also generated in a population with a documented inadequate response to laxatives.

The proposed change was therefore considered non-approvable by the CHMP. The applicant finally withdrew their claims to amend the therapeutic indication and to add the RWE data into the SmPC.

2.5. Clinical safety

NACASY Study

Overall, 89 of 170 study subjects (52.4%) reported at least one adverse event, and 38 (22.4%) were recorded as serious adverse events. The most frequent (i.e., adverse events with an incidence rate of ≥5%) are presented in Table S3. There were two cases of withdrawal syndrome that were categorized as grade 1. Adverse events considered to be related to naloxegol were reported in 23 patients (13.5%). Treatment-related adverse events were mainly gastrointestinal events, the most frequently reported being abdominal pain (n = 14, 8.2%) and diarrhea (n = 5, 2.9%). Except for a case of intestinal perforation that was categorized as grade 5, the remaining evaluable adverse events were graded 1 to 3 (Table 2).

There were two (1.2%) treatment-related adverse events that were considered serious adverse reactions: a case of grade 5 intestinal perforation and a case of grade 2 diarrhea. The intestinal perforation occurred in a 68 years-old male, diagnosed with advanced pancreatic cancer, and with a medical history of gastric bypass surgery. Shortly after initiating treatment with 25 mg of naloxegol, the patient experienced rapid deterioration of the general state, showed signs of peritonitis, sepsis and multiorgan failure, and finally died. Autopsy was not performed, and the event was categorized by the investigator as probable intestinal perforation.

Table 2. Adverse reactions to naloxegol (according to CTCAE v4.03).

Adverse Reaction	Grade 1–3		Grade 4–5		Grade NA		Total	
	N	%	N	%	N	%	N	%
Abdominal pain	10	5.9	0	0.0	4	2.4	14	8.3
Diarrhea	4	2.4	0	0.0	1	0.6	5	2.9
Fatigue	1	0.6	0	0.0	0	0.0	1	0.6
Flatulence	2	1.2	0	0.0	0	0.0	2	1.2
Gastrointestinal pain	1	0.6	0	0.0	0	0.0	1	0.6
Intestinal perforation	0	0.0	1	0.6	0	0.0	1	0.6
Nausea	2	1.2	0	0.0	0	0.0	2	1.2
Pollakiuria	1	0.6	0	0.0	0	0.0	1	0.6
Vertigo	1	0.6	0	0.0	0	0.0	1	0.6
Withdrawal syndrome	1	0.6	0	0.0	0	0.0	1	0.6

NA, not available; CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events. Grade 1: Mild; asymptomatic or mild symptoms; Grade 2: Moderate; minimal, local, or noninvasive; intervention indicated; Grade 3: Severe or medically significant but not immediately life-threatening; Grade 4: Life-threatening consequences; urgent intervention indicated; Grade 5: Death related to AE

Out of 170 patients, 20 (11.8%, 95%CI 6.9–16.6) discontinued the study due to adverse events, and, of them, 12 (7.1%, 95%CI 3.2–10.9%) were study discontinuations due to naloxegol-related adverse events. These were mainly gastrointestinal side effects, including eight cases of abdominal pain, two cases of diarrhoea, and one due to intestinal perforation; the remaining patient discontinued the study due to fatigue.

KYONAL study

A total of 28 adverse reactions mainly gastrointestinal were observed in 15.1% of the patients (19/126), 75% (21) mild, 17.9% (5) moderate and 7.1% (2) severe. Most adverse reactions (67.9%) appeared in the first 15 days of treatment with naloxegol (median of 13 days), and described as abdominal pain (13), abdominal bloating (5), diarrhoea (6), nausea (3) and dysesthesia (1). All the adverse reactions were solved. A total of six patients withdrawn from the study due to adverse reactions: abdominal pain (6), nausea (1), diarrhoea (2). The withdrawal due to adverse reactions occurred before day 15 in three patients, and between 15 and 30 days in three patients. Five patients were in treatment with 25 mg of naloxegol and one at the 12.5 mg dose. Three patients with adverse reactions were on concomitant treatment with other laxatives. Additionally, in four patients naloxegol was temporarily suspended, in one patient the naloxegol dose was reduced and in 17 patients no action was taken. During the study 53 patients died from causes related to their malignant disease considering no differences from expected cancer-related incidence. No patients withdrew from the study due to suspension of treatment with opioids.

MovE Study

At least one adverse event (AE) was reported in 43 patients (32.8%) during the study (median follow-up of patients, 4.3 months; range, 0.3–14.9), including 21 patients (16.0%) with at least one serious AE (SAE). Among the 15 AEs related to naloxegol according to investigators (11 patients, 8.4%), the most common events were gastrointestinal disorders (12 events reported in 9 patients, 6.9%) (Table 3). Among these 12 gastrointestinal AEs, 6 diarrheas were reported in 5 patients (3.8%), all of them having started naloxegol at the dose of 25 mg. One non-serious withdrawal syndrome was reported. Only one related SAE was reported (diarrhea, 0.8% of patients). Thirty AEs experienced by 22 patients (16.8%) led to naloxegol discontinuation during the study, mainly as cancer progression (8 events, 6.1% of patients) and diarrhea (4 events, 3.1% patients, all of them in the 25-mg group). Thirteen deaths were associated with AEs, without causal relationship with naloxegol as assessed by physicians.

Nalopool

In its response to the first round of outstanding issues, the applicant submitted an analysis of pooled data from the observational studies Kyonal, NACASY and MovE. Refer to Annex 2, assessment of the MAH's responses, for further details.

This pooling is most relevant for the expansion of the clinical safety experience with naloxegol in two conditions that were not investigated in the original naloxegol studies, i.e. use in cancer pain OIC patients and use concomitantly with standard laxatives. Of note, both are currently already in the Moventig label, but with warnings.

The analysis of safety data (N=427) coded adverse events using MedDRA version 23.1 across the three studies. NCI-CTCAE grades (1-5) were used in the MovE and Nacasy studies to assess intensity, while the Kyonal study used the classification: Mild, Moderate, Severe and Serious.

AE related to naloxegol (per Investigator) (AE-RPI) were reported by 11.7% of patients during the 4 week nalopool analysis period.

		STUDY							
		Kyonal		Move		Nacasy		Total	
		N	%	N	%	N	%	N	%
Adverse reactions during 4 weeks	**No**	109	86,5	120	91,6	148	87,1	377	88,3
	Yes	17	13,5	11	8,4	22	12,9	50	11,7
	Total	126	100,0	131	100,0	170	100,0	427	100,0
Serious adverse reactions during 4 week	**No**	126	100,0	130	99,2	168	98,8	424	99,3
	Yes	0	,0	1	,8	2	1,2	3	,7
	Total	126	100,0	131	100,0	170	100,0	427	100,0

The most common AE-RPI was abdominal pain which was reported by 24/427 (5.6%) patients. There were 3 serious AE-RPI: a Grade 1 diarrhea, a Grade 2 diarrhea, and a Grade 5 (fatal) intestinal perforation. AE-RPI led to discontinuation of naloxegol in 26 patients (6.1%). The most common AE-RPI leading to discontinuation were abdominal pain (n=14), diarrhea (n=6) and nausea (n=4). No other terms led to discontinuation in more than 1 patient.

		Kyonal (N=126)		Move (N=131)		Nacasy (N=170)	
		N	%	N	%	N	%
Any AR		**17**	**13,5**	**11**	**8,4**	**22**	**12,9**
Gastrointestinal disorders	Abdominal distension	5	4,0				
	Abdominal pain	9	7,1	2	1,5	13	7,6
	Constipation			1	0,8		
	Diarrhoea	4	3,2	5	3,8	5	2,9
	Eructation			1	0,8		
	Flatulence					2	1,2
	Gastrointestinal pain					1	0,6
	Intestinal perforation					1	0,6
	Nausea	3	2,4	1	0,8	2	1,2
	Vomiting			1	0,8		
General disorders and administration site conditions	Drug withdrawal syndrome			1	0,8		
	Fatigue					1	0,6
	Pain			1	0,8		
	Withdrawal syndrome					1	0,6
Metabolism and nutrition disorders	Decreased appetite			1	0,8		
Renal and urinary disorders	Pollakiuria					1	0,6
Nervous system disorders	Dysaesthesia	1	0,8				

A supplementary analysis explores the incidence of AE-RPI by concomitant laxative use during the Nalopool period. There were no notable differences in overall rates of AE-RPI, Serious AE-RPI, or AE-RPI leading to discontinuation and the profile of AE-RPI reported in patients taking concomitant laxatives was not meaningfully different to that of patients who did not take concomitant laxatives.

Nalopool Related Adverse Events (per Investigator) by Laxative Use

Adverse reactions during 4 weeks			Concomitant laxatives					
			No		Yes		Total	
			N	%	N	%	N	%
STUDY	Move	No	56	86,2	64	97,0	120	91,6
		Yes	9	13,8	2	3,0	11	8,4
		Total	65	100,0	66	100,0	131	100,0
	Nacasy	No	101	84,9	47	92,2	148	87,1
		Yes	18	15,1	4	7,8	22	12,9
		Total	119	100,0	51	100,0	170	100,0
	Total	No	157	85,3	111	94,9	268	89,0
		Yes	27	14,7	6	5,1	33	11,0
		Total	184	100,0	117	100,0	301	100,0

Nalopool Serious Related Adverse Events (per Investigator) by Laxative Use

Serious adverse reactions during 4 week			Concomitant laxatives					
			No		Yes		Total	
			N	%	N	%	N	%
STUDY	Move	No	64	98,5	66	100,0	130	99,2
		Yes	1	1,5	0	,0	1	,8
		Total	65	100,0	66	100,0	131	100,0
	Nacasy	No	117	98,3	51	100,0	168	98,8
		Yes	2	1,7	0	,0	2	1,2
		Total	119	100,0	51	100,0	170	100,0
	Total	No	181	98,4	117	100,0	298	99,0
		Yes	3	1,6	0	,0	3	1,0
		Total	184	100,0	117	100,0	301	100,0

Nalopool Related Adverse Events (per Investigator) Leading to Discontinuation by Laxative Use

Presence of adverse reaction leading to discontinuation			Concomitant laxatives					
			No		Yes		Total	
			N	%	N	%	N	%
STUDY	Move	No	59	90,8	64	97,0	123	93,9
		Yes	6	9,2	2	3,0	8	6,1
		Total	65	100,0	66	100,0	131	100,0
	Nacasy	No	108	90,8	50	98,0	158	92,9
		Yes	11	9,2	1	2,0	12	7,1
		Total	119	100,0	51	100,0	170	100,0
	Total	No	167	90,8	114	97,4	281	93,4
		Yes	17	9,2	3	2,6	20	6,6
		Total	184	100,0	117	100,0	301	100,0

2.5.1. Discussion on clinical safety

In its response to the first round of outstanding issues, the applicant submitted an analysis of pooled data from the observational studies Kyonal, NACASY and MovE (Nalopool). This pooling is most relevant for the expansion of the clinical safety experience with naloxegol in two conditions that were not investigated in the original naloxegol studies, i.e. use in cancer pain OIC patients and use concomitantly with standard laxatives. Of note, both are currently already in the Moventig label, but with warnings.

In the 4 week analysis period, adverse reactions related to the use of naloxegol were identified in 11% of patients, the most common being abdominal pain. In 6% of patients, adverse reactions led to the discontinuation of naloxegol treatment. In total 3 RPI serious adverse reactions were identified. The safety pool contained 427 patients, which is considered sufficiently large. For comparison, naldemedine (Rizmoic) data presented in the Rizmoic SmPC were generated in 2 clinical trials where in total 155 cancer pain patients received naldemedine.

A supplementary analysis explored the incidence of adverse reactions by concomitant laxative use. According to the MAH there were no notable differences in overall rates of AE-RPI, Serious AE-RPI, or AE-RPI leading to discontinuation and the profile of AE-RPI reported in patients taking concomitant laxatives was not meaningfully different to that of patients who did not take concomitant laxatives. The relative occurrence of adverse reactions was numerically lower in those patients taking concomitant laxatives (5%) compared to those patients not taking concomitant laxatives (15%). A similar observation was made with regard to serious adverse reactions which all three occurred in those patients that were not taking concomitant laxatives. Likewise, discontinuations due to adverse reactions were 9% in the patient population not on concomitant laxatives and 3% in the population that used concomitant laxatives. These results indicated that naloxegol can be safely used concomitantly with standard laxatives.

Altogether, the safety analysis shows that no new safety concerns were identified and that adverse reactions due to naloxegol treatment occurred at a low frequency in cancer pain OIC patients. In addition, the number of serious adverse reactions was very limited. Concomitant use of standard laxatives did not increase safety concerns, and numerically, adverse reactions occurred less frequently in patients that used concomitant laxatives. Accodingly the changes made to the SmPC in 4.2 (Moventig may be used with or without laxatives) and in 4.4. deletion of a precautionary statement in OIC patients with cancer related pain due to limited clinical experience can be agreed from a safety perspective. Further, adding a sentence in 4.2 of the SmPC that Moventig treatment should be withdrawn when systemic opioid therapy is stopped is agreed with due to the mechanism of action of the drug being a mu-opioid receptor antagonist.

No clinical data were submitted in support of the proposed change in therapeutic indication.

2.5.2. Conclusions on clinical safety

Data from the individual observational studies (Kyonal, NACASY and MovE) and the analysis of pooled data (Nalopool) confirmed the safety of naloxegol in the treatment of OIC in cancer pain patients, with or without concomitant laxatives. Since the bulk of safety data for naloxegol had been generated in controlled clinical trials in non-cancer patients, a safety based warning was issued in the Moventig SmPC, stating that the clinical experience in cancer pain patients was limited. Based on the safety data from the Nanopool safety set, which comprised 427 patients and which was reassuring with regard to safety of naloxegol in this patient population, it is agreed that the following statement is removed from the SmPC:

"Cancer related pain

There is limited clinical experience with the use of naloxegol in OIC patients with cancer-related pain. Therefore, caution should be used when prescribing naloxegol to such patients (see section 4.3)."

Safety was also compared in patients using naloxegol with and without concomitant laxatives, in the Nanopool dataset. The safety profile in patients taking concomitant laxatives was reassuring and numerically less adverse events related to naloxegol were observed in patients concomitantly taking standard laxatives compared to those that did not. In current label, it was recommended to halt standard laxatives until the naloxegol effect was established. However, based on the reassuring observational study data, there is no scientific rationale to further support this statement and the following change in section 4.2 is considered acceptable:

Moventig may be used with or without laxatives. Moventig treatment should be withdrawn when systemic opioid therapy is stopped.

Altogether, the safety of naloxegol in cancer pain OIC patients, with or without concomitant laxatives, is confirmed to be reassuring by data from observational studies.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The MAH submitted an updated RMP version with this application.

The PRAC considered that the risk management plan version 8.2 is acceptable.

The CHMP endorsed this advice without changes.

The CHMP endorsed the Risk Management Plan version 8.2 with the following content:

Safety concerns

Summary of the safety concerns

Important identified risks	Opioid Withdrawal Syndrome Clinically Important Gastrointestinal Events Gastrointestinal perforation Interactions with drugs modulating CYP3A4 and P-gp activities
Important potential risks	Haemodynamic changes potentially leading to serious cardiovascular events (including effects on blood pressure and syncope) Interference with opioid mediated analgesia

Missing information	Use in high risk CV patients Safety beyond one year of exposure Use in methadone-treated patients Use in pregnancy and lactation Use in patients over 75 years of age Use in patients with severe renal impairment Use in patients with severe hepatic impairment

Pharmacovigilance plan

Ongoing and planned additional pharmacovigilance activities

Study/Status	Summary of objectives	Safety concerns addressed	Milestones (for EMA)	Due dates (for EMA)
Category 3 - Required additional pharmacovigilance activities				
D3820R00008 United States Post-Marketing Observational Cardiovascular Safety Study in Patients taking naloxegol (Retrospective, new-user cohort design)	To assess the overall risk of Major Adverse Cardiovascular Events (MACE) among naloxegol treated patients compared to that among patients on non-PAMORA prescription OIC treatments. Oral non-naloxegol PAMORAs will be included as these agents become available on the market.	Haemodynamic changes potentially leading to serious cardiovascular events (including effects on blood pressure and syncope) Use in high risk CV patients Safety beyond one year of exposure	**Interim Data** **Final data**	Annual reports. 4Q 2023

Risk minimisation measures

Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Opioid withdrawal syndrome	**Routine risk minimisation measures**: SmPC Section 4.8, Undesirable effects	**Additional pharmacovigilance activities**
	SmPC Section 4.4 recommends caution when prescribing naloxegol to patients with clinically important disruptions to the blood-brain barrier, taking into account their individual benefit-risk balance with observation for potential CNS effects, such as symptoms of opioid withdrawal.	**None**
	SmPC Section 4.5, concomitant use of other narcotic antagonists not recommended.	
	SmPC Section 4.9, recommends that patients who have an overdose of naloxegol be monitored closely for potential evidence of opioid withdrawal symptoms.	
	PIL Section 4: Possible side effect PIL Section 2, Take special care	
Clinically important gastrointestinal events	**Routine risk minimisation measures:** SmPC Section 4.8, Undesirable effects	**Additional pharmacovigilance activities**: **None**
	SmPC Section 4.4 advises patients to promptly report severe, persistent or worsening GI symptoms to their physician. Consideration may be given to lowering the dose to 12.5 mg in patients experiencing severe GI events.	
	PIL Section 2, Take special care with naloxegol	
	PIL Section 4, Possible side effects	

GI perforation	**Routine risk minimisation measures:** SmPC Section 4.3, Contraindications Section 4.4, Special warnings and special precautions for use Section 4.8, Undesirable effects **Routine risk minimisation activities recommending specific clinical measures to address the risk:** SmPC Section 4.3 states that naloxegol is contraindicated in patients with known or suspected GI obstruction and in patients at increased risk of recurrent obstruction. In addition, naloxegol should not be used in patients with cancer pain who are at heightened risk of GI perforation**.** SmPC Section 4.4 recommends caution regarding the use of naloxegol in patients with any condition which might result in impaired integrity of the gastrointestinal tract wall. These patients are advised to discontinue therapy with naloxegol and promptly notify their physician if they develop unusually severe or persistent abdominal pain. PIL Section 2, What you need to know before you take naloxegol PIL Section 2, Take special care with Naloxegol PIL Section 4, Possible side effects **Other routine risk minimisation measures beyond the Product Information:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Targeted follow-up questionnaire/ intake mechanism for post-marketing reports of GI perforation **Additional pharmacovigilance activities: None**

Interactions with drugs modulating CYP3A4 and P-gp activities	**Routine risk communications:** SmPC Section 4.2 states that no dose adjustment is necessary for concomitant use of naloxegol with dual Pgp/weak CYP3A4 inhibitors SmPC Section 4.3 states that concomitant use with dual Pgp/strong CYP3A4 inhibitors can significantly increase exposure to naloxegol and is contraindicated. SmPC Section 4.4 reinforces the warnings included in Section 4.2 In addition it states that grapefruit has been classified as a CYP3A4 inhibitor. No data is available of the concomitant use of naloxegol and grapefruit, so it is recommended that concomitant use is avoided and considered only in consultation with a healthcare provider. SmPC Section 4.5 includes a summary of the data available relating to this risk including that grapefruit has been classified as a potent CYP3A4 inhibitor when consumed in large quantities. No data is available of the concomitant use of naloxegol and grapefruit, so it is recommended that concomitant use is avoided and considered only in consultation with a healthcare provider.	**Additional pharmacovigilance activities**: **None**

	PIL Section 2 warns that naloxegol should not be taken if the patient is taking other medications such as ketoconazole or itraconazole (to treat fungal infections), clarithromycin or telithromycin (antibiotics) or ritonavir, indinavir or saquinavir (to treat HIV). It also warns that patients should not drink large amounts of grapefruit juice whilst taking naloxegol. **Routine risk minimisation activities recommending specific clinical measures to address the risk**: SmPC Section 4.2 details recommends patients concomitantly taking moderate CYP3A4 inhibitors or dual Pgp/moderate CYP3A4 inhibitors should start on a dose of 12.5 mg, which can be increased to 25 mg if this is well tolerate by the patient. SmPC Section 4.5 reinforces the warning in Section 4.2 that the starting dose of patients concomitantly taking moderate CYP3A4 inhibitors is 12.5 mg, and that this can be increased if well tolerated. PIL Section 3 warns that the patient's doctor may tell them to take a lower dose of 12.5 mg if they take diltiazem or verapamil (for high blood pressure or angina).	
Haemodynamic changes potentially leading to serious cardiovascular events (including effects on blood pressure and syncope)	**Routine risk minimisation measures:** None	**Additional pharmacovigilance activities** **Study D3820R00008** Naloxegol US PMR CV Safety

Interference with opioid mediated analgesia	**Routine risk minimisation measures:** SmPC Section 4.4 recommends caution when prescribing naloxegol to patients with clinically important disruptions to the blood-brain barrier taking into account their individual benefit-risk balance with observation for potential CNS effects, such as symptoms of reversal of analgesia. SmPC Section 4.9, monitor closely for potential evidence of opioid withdrawal symptoms or reversal of central analgesic effect	**Additional pharmacovigilance activities** **None**
afety beyond one year of exposure	**Routine risk minimisation measures:** None	**Additional pharmacovigilance activities** **Study D3820R00008** Naloxegol US PMR CV Safety
Use in high risk CV patients	**Routine risk minimisation measures:** None	**Additional pharmacovigilance activities** **Study D3820R00008** Naloxegol US PMR CV Safety
Use in methadone-treated patients	**Routine risk minimisation measures:** SmPC Section 4.4: Concurrent methadone use PIL Section 2 states that patients should talk to their doctor, pharmacist or nurse before taking Moventig if they are taking methadone	**Additional pharmacovigilance activities** **None**

Use in pregnancy and lactation	**Routine risk minimisation measures:** SmPC Section 4.6 states that there are limited data from the use of naloxegol in pregnant women, and that it is unknown whether naloxegol is excreted in human milk. PIL Section 2 states that Moventig is not recommended for use during pregnancy or during breast-feeding.	**Additional pharmacovigilance activities** **None**
Use in patients over 75 years of age	**Routine risk minimisation measures:** SmPC Section 4.2 states that no dose adjustment is recommended based on age.	**Additional pharmacovigilance activities** **None**
Use in patients with severe renal impairment	**Routine risk minimisation measures:** SmPC Section 4.2 states that the starting dose for patients with moderate or severe renal insufficiency is 12.5 mg. If side effects impacting tolerability occur, naloxegol should be discontinued. The dose can be increased to 25 mg if 12.5 mg is well tolerated by the patient. PIL Section 3 states that the patient's doctor may advise a lower dose if the patient has kidney problems	**Additional pharmacovigilance activities** **None**
Use in patients with severe hepatic impairment	**Routine risk minimisation measures:** SmPC Section 4.2 states that use in patients with severe hepatic impairment is not recommended. SmPC Section 4.4 states that naloxegol has not been studied in patients with severe hepatic impairment and use of naloxegol is not recommended in such patients.	**Additional pharmacovigilance activities** **None**

2.7. Update of the Product information

Please refer to the Product Information containing all agreed changes.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package

leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

The changes to the PIL are considered to be minimal with no impact on readability, no additional user testing is deemed necessary.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Opioid-induced bowel dysfunction is a complication of opioid therapy, in which constipation is the most common and problematic symptom (Farmer et al., 2019).

Opioids are a class of potent analgesics, and their use has increased markedly in recent years. Opioids are associated with a variety of bothersome side effects such as sedation, lethargy and pruritus, notwithstanding the considerable risk of addiction. Opioids also adversely impact the sensorimotor function of the gastrointestinal tract, via the action of exogenous opioid agonists, on the enteric nervous system. Such adverse effects limit dose escalation and can necessitate a switch in opioids or even cessation of therapy. The term opioid-induced bowel dysfunction (OIBD) encompasses a spectrum of symptoms including nausea, vomiting, bloating, gastro-oesophageal reflux-related symptoms and constipation. Opioid-induced constipation (OIC) is the most common subtype of OIBD that occurs in 51–87% of patients receiving opioids for cancer and between 41–57% patients receiving opioids for chronic non-cancer pain (Farmer et al., 2019).

3.1.2. Available therapies and unmet medical need

The pathophysiology of opioid-induced constipation is multi-faceted and 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. 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 (Farmer et al., 2019).

Standard laxatives, such as osmotic agents (macrogol) and stimulants (bisacodyl, picosulphate and senna) are good first-line choices in the management of OIC (Farmer et al., 2019).

Opioid-receptor antagonists can alleviate the adverse effects of opioids on GI functions, but their central analgesic effects may also be antagonised if they cross the blood-brain barrier. The most readily well-known example is naloxone, commonly used as an intravenous reversal agent in the context of opioid over-dosing. Agents that block mu-opioid receptors in the GI tract, but do not enter the central nervous system (CNS), are expected to treat OIBD without diminishing central analgesic actions. Several opioid antagonists with local action within the gut or (outside the CNS) peripherally-acting mu-opioid receptor antagonists (PAMORAs) have become available such as methylnaltrexone, naldemedine and naloxegol (Farmer et al., 2019).

3.1.3. Main clinical studies

In the initial marketing authorisation application, naloxegol has been demonstrated in randomised, double blind phase 3 clinical studies to be safe and efficacious in the treatment of OIC in patients with non-cancer pain related OIC. A clinically relevant and statistically significant effect was observed in the laxative inadequate subgroup (LIR) of patients. In the non-LIR subgroup, no such effect was observed. 66% of non-LIR patients had tried laxatives in the past (within 6 months) but had stopped them for various reasons.

Moventig is thus currently indicated for the treatment of opioid-induced constipation (OIC) in adult patients who have had an inadequate response to laxative(s). The SmPC specifies how this inadequacy of response was established in the clinical studies supporting the therapeutic indication.

In the current type II variation, the MAH proposes to change the indication as follows: Moventig is indicated for the treatment of opioid-induced constipation (OIC) in adult patients who have previously been treated with a laxative. The applicant motivated the change in 4.1 stating that the new indication better reflects the class recommendation for PAMORAs (De Giorgio, et al., 2021) and how Moventig is used in clinical practice.

No new clinical data have been submitted to support such expansion of the indication to patients with a non-documented response to laxatives. Results from the observational studies (see below) MovE, NACASY and KYONAL were also generated in a population with a documented inadequate response to laxatives.

In support of the changes proposed in section 4.2 and 4.4, a pooled analysis of safety and efficacy data was submitted. This pool comprised clinical data from three observational studies, MovE, NACASY and Kyonal.

3.2. Favourable effects

Non cancer-pain OIC patients were included in the pivotal phase 3 studies for Moventig. At the time of the initial marketing authorisation, a trial in this patient population was early terminated because of recruitment issues. However, cancer-pain OIC patients are included in the current label since the effect of naloxegol was and is not considered to be different in those patients, but a (safety) warning on the limited clinical experience in this patient population was included in the SmPC, which the applicant wishes to remove in current variation. Data from three observational studies (MovE, NACASY and Kyonal) further confirmed that naloxegol is efficacious in a real world setting of OIC treatment in cancer-pain related patients.

The concomitant use of laxatives was not allowed in the pivotal naloxegol studies in non-cancer pain OIC studies and a recommendation to halt standard laxatives until the effect of naloxegol is determined is currently present in the SmPC. In cancer-pain OIC patients, it is accepted that an add-on treatment is investigated, since the origin of constipation in these patients might not solely be due to opioid use. Real world data from three observational studies confirmed that naloxegol use concomitantly with standard laxatives is efficacious.

3.3. Uncertainties and limitations about favourable effects

In the data package submitted, the use of naloxegol in combination with standard laxatives was only investigated in observational studies in cancer pain patients, not in patients suffering from OIC induced by opioid use for non-cancer pain or in controlled clinical trials. However, it is not expected that the

effect of concomitant laxative use would be different in non-cancer pain patients, also considering that naloxegol and standard laxatives have a different mode of action.

3.4. Unfavourable effects

Data from three observational studies (MovE, NACASY and Kyonal) demonstrated that naloxegol is safe in a real world setting of OIC treatment in cancer-pain patients. The pooled safety population for the 4 week period that was assessed comprised 427 patients.

In cancer-pain OIC patients, it is accepted that an add-on treatment is investigated, since the origin of constipation in these patients might not solely be due to opioid use. Real world data from the three observational studies demonstrated that naloxegol use concomitantly with standard laxatives is safe in these patients. Adverse reactions considered related to naloxegol use, per investigator, were numerically lower in patients using naloxegol combined with standard laxatives compared to when naloxegol was used alone.

3.5. Uncertainties and limitations about unfavourable effects

The data relevant for the changes with regard to cancer-pain experience and concomitant laxative use come from real word studies and not from controlled clinical trials. However, these data mainly serve to establish the safety of naloxegol use in both conditions, since the bulk of the clinical efficacy and safety data have already been provided in two similar controlled phase 3 studies in patients with OIC and non-cancer related pain. It is considered that the real world data are valuable in expanding the safety experience in cancer pain OIC patients and in patients taking concomitant standard laxatives.

The use of naloxegol in combination with standard laxatives was only investigated in observational studies in cancer pain patients, not in patients suffering from OIC induced by opioid use for non-cancer pain. In cancer pain patients, concomitant use with standard laxatives did not reveal additional safety issues related to naloxegol. It is not expected that this would be different in non-cancer pain patients, also considering that naloxegol and standard laxatives have a different mode of action.

3.6. Benefit-risk assessment and discussion

3.6.1. Importance of favourable and unfavourable effects

No clinical data were submitted in support of the change in therapeutic indication. No favourable or unfavourable effects therefore could be identified for the modified indication.

Clinical experience with naloxegol in cancer pain OIC patients with or without concomitant use of standard laxatives confirmed it was efficacious and could be used safely in this patient population.

3.6.2. Balance of benefits and risks

The MAH proposed to change the approved therapeutic indication as follows: Moventig is indicated for the treatment of opioid-induced constipation (OIC) in adult patients who have previously been treated with a laxative, removing the restriction of the indication to laxative inadequate responders.

The applicant motivated the change in 4.1 stating that the new indication better reflects the class recommendation for PAMORAs (De Giorgio, et al., 2021) and the way Moventig is used in clinical practice. The original Moventig data only supported a positive B/R in an OIC population with a

documented inadequate response to laxatives, and not in the population where such inadequate response was not documented, even though many of the latter patients had used a standard laxative before at some point. Results from the observational studies MovE, NACASY and KYONAL were also generated in a population with a documented inadequate response to laxatives. No new clinical data were submitted to support the expansion of the indication to patients with a non-documented response to laxatives.

In the absence of new evidence, the proposed change in the wording of the therapeutic indication was not considered acceptable by the CHMP. The MAH withdrew the change to the indication in the course of the procedure and the therapeutic indication will therefore remain limited to patients with a documented inadequate response to laxatives.

Data from the individual observational studies and the analysis of pooled data confirmed the efficacy of naloxegol in the treatment of OIC in cancer pain patients, with or without concomitant laxatives. Since the bulk of efficacy data for naloxegol had been generated in controlled clinical trials, and a similar effect was expected in cancer pain patients, the expansion of clinical experience in cancer pain patients with data from observational studies is acceptable, since they only serve to further support an already granted indication. Accordingly, the applied changes to 4.2 (Moventig may be used with or without laxatives) and 4.4 (deletion of precautionary statement in OIC patients with cancer) are considered acceptable. Furthermore, the removal of Safety in Patients with Cancer Pain as Missing information in the RMP and editorial changes to the product information were agreed with by the committee.

The applicant applied to include data from supporting observational studies Kyonal, NACASY and MovE into 5.1 of the SmPC. However, the CHMP did not agree with this approach taking into consideration the SmPC guideline stating that "It may be appropriate to provide limited information, relevant to the prescriber, such as the main results (statistically compelling and clinically relevant) regarding pre-specified end points or clinical outcomes in the major trials and giving the main characteristics of the patient population. Such information on clinical trials should be concise, clear, relevant and balanced, and should summarize evidence from relevant studies supporting the indication." As a consequence, the MAH withdrew their claim to update 5.1 of the SmPC.

The CHMP, whilst agreeing on the supporting evidence for the changes in 4.2 and 4,4. as outlined in this report disagreed to include this RWE into 5.1 of the SmPC. The MAH agreed with this approach.

3.6.3. Additional considerations on the benefit-risk balance

N/A

3.7. Conclusions

The MAH submitted a variation application under category C.1.6.a of the variation classification Guideline with the scope to "Update of sections 4.1, 4.2, 4.4, 4.8, 5.1, and 5.2 of the SmPC in order to update information regarding the use of naloxegol in OIC patients with cancer-related pain based on real-world data from non-interventional studies (NACASY, KYONAL, and MOVE studies), post-marketing data, and literature. The Package Leaflet is updated accordingly. The RMP version 8 has also been submitted. In addition, the MAH took the opportunity to implement editorial changes to the SmPC.

The variation requested amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP)."

Based on the assessment of the data contained in the application, the CHMP is of the view that the following changes to the MA should be introduced "Update of sections 4.2 and 4.4 of the SmPC based

on real-world data from non-interventional studies (NACASY, KYONAL, and MOVE studies), post-marketing data, and literature on the use of naloxegol in OIC patients with cancer-related pain. The Package Leaflet is updated accordingly.

The RMP version 8.2 has also been agreed. In addition, the MAH took the opportunity to implement editorial changes to the SmPC" These changes fall under category C.1.4 of the variation classification Guideline.

During the procedure, the MAH updated the product information accordingly.

The overall B/R of Moventig in the existing indication remains positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Update of sections 4.2 and 4.4 of the SmPC based on real-world data from non-interventional studies (NACASY, KYONAL and MOVE studies), post-marketing data, and literature on the use of naloxegol in OIC patients with cancer-related pain. The Package Leaflet is updated accordingly.

The RMP version 8.2 has also been submitted. In addition, the MAH took the opportunity to implement editorial changes to the SmPC.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I and IIIB and to the Risk Management Plan are recommended.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion 'Moventig H/C/002810/II/0039.