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

Manuel Cobo Dols ,[1,2] Carmen Beato Zambrano,[3] Luis Cabezón-Gutiérrez,[4] Rodolfo Chicas-Sett,[5] María Isabel Blancas López-Barajas,[6] Francisco Javier García Navalón,[7] José Luis Fírvida Pérez,[8] Gala Serrano Bermúdez,[9] Pilar Togores Torres,[10] Ignacio Delgado Mingorance,[11] Alexandra Giraldo Marín,[12] Anna Librán Oriol,[13] Alfredo Paredes Lario,[14] Pedro Sánchez Mauriño,[15] Oliver Higuera Gómez,[16] Diana Moreno Muñoz,[17] Ibone Huerta González,[18] Almudena Sanz-Yagüe,[18] Begoña Soler López [19]

For numbered affiliations see end of article.

Correspondence to
Dr Manuel Cobo Dols, Hospital Regional Universitario de Málaga, Málaga, Spain; manuelcobodols@yahoo.es

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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

first declared in 2016 as a new category in the Rome IV criteria.[1 2] OIC affects up to 41%–57% of patients with pain,[3–10] and up to 87% of patients with pain and cancer.[10–13]

Opioids are prescribed to patients with cancer for the control of pain. OIC is an adverse effect that persist throughout the opioid treatment period, unlike other side effects related to opioid use which disappear over time, such as nausea, vomiting and sedation.[3] Another aspect is that the opioid dose inducing OIC is about four times lower than the dose to get an analgesic effect, therefore, the dose reduction is unlikely to reduce constipation.[14] In spite of this fact, in up to 60% of the patients, the opioid dose is reduced by the physician or by the patient in the hope that this will cause the symptom to disappear, leading to an inadequate pain control.[12 15]

OIC is a symptom hard to treat, as treatment based on hygiene dietary measures and laxatives is not effective in many patients.[16 17] Different Medical Societies have published guidelines for the management of constipation and OIC in patients with cancer and recommend treatment with naloxegol in patients with laxatives inadequate response (LIR).[13 18–21]

Naloxegol is a pegylated naloxone derivative approved in 2014 for the treatment of OIC in adult patients with non-cancer pain by the Food and Drug Administration, and by the European Medicines Agency (EMA) for use in patients with or without cancer. The drug is indicated for the treatment of OIC in adult patients who have had an inadequate response to laxative(s). Up till now only small retrospective studies have been completed for the treatment of OIC in patients with cancer, and the long-term efficacy and safety profile of naloxegol for these patients are unknown.[22]

An interim analysis of the study with the per protocol sample at 3 months of follow-up has been previously published.[23] The objective of this study was to analyse the efficacy and safety of naloxegol in patients with cancer in a real-world study at twelve months. The primary efficacy endpoint was to assess the impact of naloxegol on constipation-related quality of life (QOL).

METHODS

An observational study with 12 months of follow-up was designed with six follow-up visits (baseline-15 days-1 month-3 months-6 months-12 months), from 21 September 2017 (first patient first visit) to 11 November 2019 (last patient last visit).

Sixteen investigators of 12 Spanish provinces participated in the study: 12 medical oncologists, 2 from the palliative care unit and two radiation oncologists.

Written informed consent was obtained from all patients.

Patient screening

The objective population were patients with cancer and a confirmed diagnosis of OIC with LIR.

OIC was defined based on the Rome IV criteria.[1 2] LIR was 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 inclusion criteria were: (1) patients over 18 years of age; (2) a diagnosis of active oncological disease requiring treatment with opioids for pain control; (3) symptoms of OIC at the time of screening (an average of <3 spontaneous bowel movements (SBM) a week with associated symptoms of constipation in at least 25% of the SBM; (4) LIR for the treatment of OIC, and indication for the treatment with naloxegol; (5) Karnofsky performance status score ≥50; (6) outpatients at study entry; (7) patients with sufficient capacity to complete the data corresponding to the symptoms and QOL scales and (8) patient's signed informed consent.

Any patient with any contraindication described in the Summary of Product Characteristics of naloxegol and patients with cognitive impairment or uncooperative were excluded.

The patients completed a diary card, recording the number of weekly SBM, any adverse reactions to naloxegol and the use of rescue medication.

The primary endpoint was the assessment of the impact of naloxegol in the constipation-related QOL outcome, measured by the patient assessment of constipation QOL questionnaire (PAC-QOL validated Spanish version). The questionnaire comprises 28 questions classified into four subscales: worries and concerns, physical discomfort, psychosocial discomfort and satisfaction. The severity of each symptom was referred to the last 2 weeks and scored on a 0–4-point scale. The total and subscales scores were calculated by averaging the item scores, where a higher PAC-QOL score means poorer QOL. Changes in the total or subscale scores of ≥0.5 points were considered clinically relevant.[24]

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

The constipation symptoms were measured by the PAC symptoms (PAC-SYM) referred to the last 2 weeks (PAC-SYM, validated Spanish version). This instrument consists of 12 questions with three subscales (stool, rectal and abdominal symptoms), scoring the severity of each symptom on a 0–4-point scale where 4 corresponds to greatest intensity. The total and subscale scores were calculated from the average of the item scores. Changes in the total or subscale scores of ≥0.5 points were considered clinically relevant. A higher PAC-SYM score means poorer symptoms.[25]

The global health related QOL was measured at baseline, six and 12 months by means of the generic

Table 1 Sociodemographic and clinical history data of the patients included in the study

		% (n) or mean (95% CI) N=126
Age		61.5 (95% CI 59.4 to 63.7)
Age groups	≤65 years	57.9% (73)
	>65 ≤75 years	31% (39)
	>75 years	11.1% (14)
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 (BMI), kg/m^2		25 (24.2–25.8)
Classification according to BMI	Cachexia (<20 kg/m^2)	10.3% (13)
	Normal (≥20 to <25 kg/m^2)	42.9% (54)
	Overweight (≥25 to <30 kg/m^2)	35.7% (45)
	Obese (≥30 kg/m^2)	11.1% (14)
Karnofsky performance status (%)		77.5 (95% CI 75.4 to 79.7)
Patients with system organ class disorders on treatment at study entry	Blood and lymphatic system	4.8% (6)
	Cardiac	25.4% (32)
	Endocrine	15.1% (19)
	Gastrointestinal	5.6% (7)
	Musculoskeletal and connective	19% (24)
	Neoplasms	88.9% (112)
	Nervous system	2.4% (3)
	Psychiatric	10.3% (13)
	Renal and urinary	11.1% (14)
	Respiratory	16.7% (21)
	Skin and subcutaneous tissue	2.4% (3)
Organ affected by the cancer	Lung	35.7% (45)
	Breast	16.7% (21)
	Gastrointestinal	10.3% (13)
	Prostate	8.7% (11)
	Other	28.6% (36)
Time from cancer diagnosis (months)		34.7 (95% CI 23.5 to 45.9)
Presence of metastases		67.5% (85)

questionnaire EuroQoL-5D-5L with five questions for the measurement of five dimensions and a Visual Analogue Scale (VAS) measuring the global health (0–100 mm) where a higher score represents a better health status.[26 27]

The safety of naloxegol treatment was assessed from the adverse reactions observed.

Information was collected on sociodemographic and medical history as described in table 1.

The patients scored at each visit, their pain intensity on a VAS with 0 score meaning no pain and 10 points the maximum pain.

The mean stool consistency was scored using the 7-point Bristol scale.[28]

Sample size calculation

From the primary efficacy endpoint, it was considered clinically significant, changes in the total PAC-QOL score of 0.5 points or higher from baseline or between periods.[24]

A sample of 126 patients was estimated to afford a statistical power of 98% in detecting differences of 0.5 points in the PAC-QOL, with a precision of ±0.03 points in the 95% CI of the differences between means, in paired comparisons between periods, with a two-tailed alpha significance criterion of 0.05. (Sample Power, SPSS).

Statistical analysis

The descriptive analysis included the summary of frequencies and percentages for the qualitative variables, and the mean, SD, and 95% CIs, for quantitative variables. The Fisher exact test or the χ^2 test in the case of qualitative variables, and the Student's t-test for the comparison of independent groups if quantitative variables were applied.

The analysis of the quantitative variables over time was based on analysis of variance for repeated measures, applying Bonferroni or Games Howell corrections for the control of error due to multiple comparisons. 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 method for imputation of missing data in lost to follow-up patients. A sensitivity analysis was performed with the per protocol data. Statistical significance was stablished at 0.05 level. For the statistical analysis the IBM-SPSS V.25.0 package was used. The EMA guidelines for the evaluation of medicinal products for the treatment of OIC were followed.[29]

RESULTS

A total of 126 patients were included. Clinical and sociodemographic data are described in table 1. Eighty-one patients (64.3%) were receiving concomitant treatment at study entry.

Cancer was the main cause of chronic pain (88.9%; n=112). The opioids prescribed for the management of pain and related to the OIC were fentanyl in 74 patients (58.7%), morphine in 33 patients (26.2%), oxycodone in 15 patients (11.9%), tapentadol in three patients (2.4%) and methadone in one patient (0.8%), at each product specifications doses.

About 27.8% of the patients (n=35) had a prior history of constipation, with a mean duration of 3.1 months (95% CI 2 to 4.2) with OIC.

Constipation-related QOL

A clinically and statistically significant improvement was observed in all the PAC-QOL scores from baseline

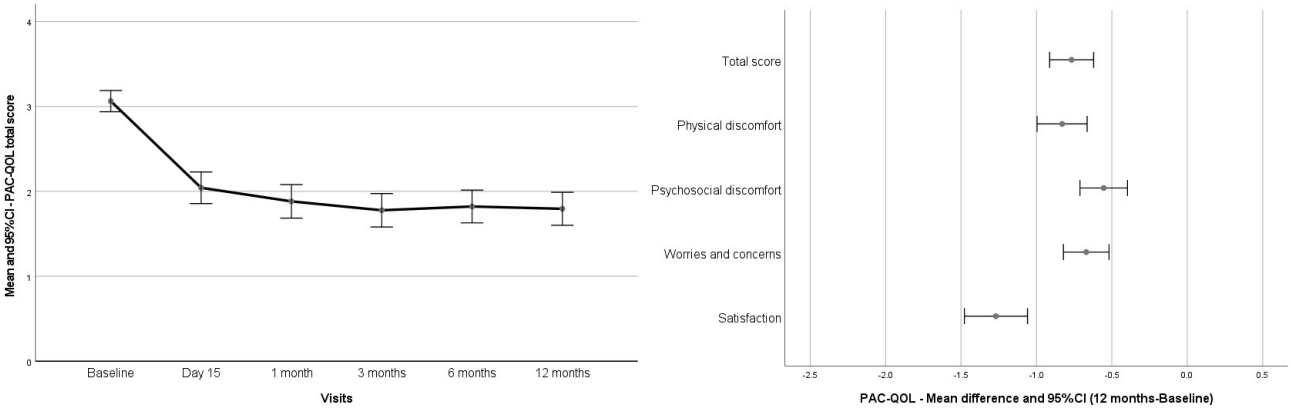

Figure 1 Patient's assessment of constipation quality of life (PAC-QOL) questionnaire evolution from baseline to month 12 of follow-up.

and between all the subsequent visits (p<0.0001). Represented in the figure 1 are the evolution of the total score and the improvement from baseline to month 12. The proportion of patients with clinically relevant improvement in the total PAC-QOL score was 50.8% (n=64) after 15 days, 60.3% (n=76) after 1 month, 61.9% (n=78) after 3 months, 57.1% (72) at 6 months and 58.7% (n=74) at month 12.

Response to naloxegol treatment

A total of 71.4% (95% CI 62.7% to 79.1%) of the patients (n=90) responded to treatment with naloxegol after 15 days, 74.6% (95% CI 66.1% to 81.9%) after 1 month (n=94), 76.2% (95% CI 67.8% to83.3%) at month 3 (n=96), 77% (95% CI 68.7% to 84%) at month 6 (n=97), and 77.8% (95% CI 69.5% to 84.7%) at month 12 (n=98). According to whether the patients received concomitant laxative therapy during the study and the naloxegol dose, the response rates were analysed (figure 2). No significant response rate differences were demonstrated by dose and/or concomitant laxative use.

As the response to laxatives could differ between patients with different cancer this point was analysed but no significant differences in response to treatment were shown. Also, no significant differences in response rate by different patient's baseline characteristics were found (online supplemental material 1).

Constipation-related symptoms

Clinically and statistically significant improvement (p<0.0001) was observed in all the PAC-SYM scores from baseline and between all the subsequent visits (figure 3). The proportion of patients with clinically relevant improvement in the total PAC-SYM score was 54.8% (n=69) after 15 days, 63.5% (n=80) after 1 month, 64.3% (n=81) after 3 months, 64.3% (n=81) at month 6% and 65.9% (n=83) at month 12.

Both PAC-SYM and PAC-QOL improvements were correlated to increases in the frequency of SBM (p<0.001).

Treatments for OIC

The last treatment prescribed for the management of OIC from its diagnosis to study entry for which an inadequate response was observed were: macrogol (31%, 39), lactulose (30.2%, 38), bisacodyl (8.7%, 11), paraffin oil (4%, 5), magnesia (4%, 5), sennosides (3.2%, 4), polyetilenglycol (2.4%, 3), sodium picosulfate (0.8%, 1), lactitol (0.8%, 1), plantago ovata (0.8%, 1), combinations of two laxatives 7.9% (10) and not described in 6.3% (8).

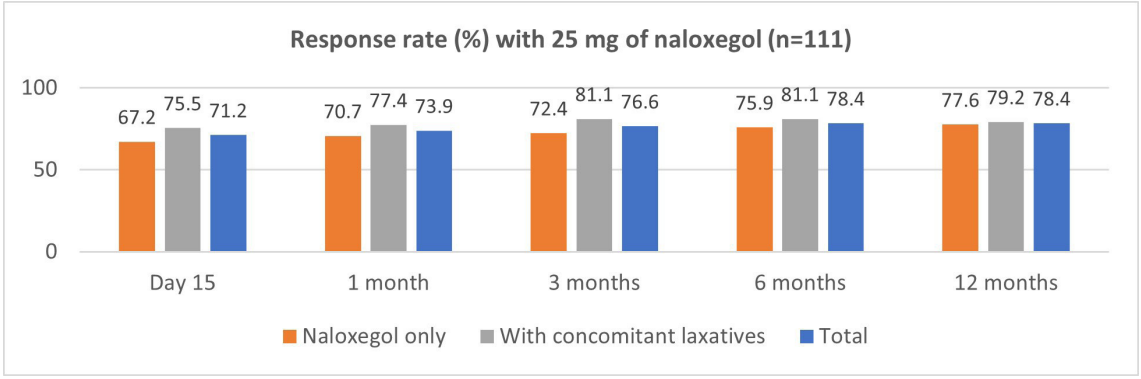

Figure 2 Response rate to naloxegol according to use of concomitant laxative.

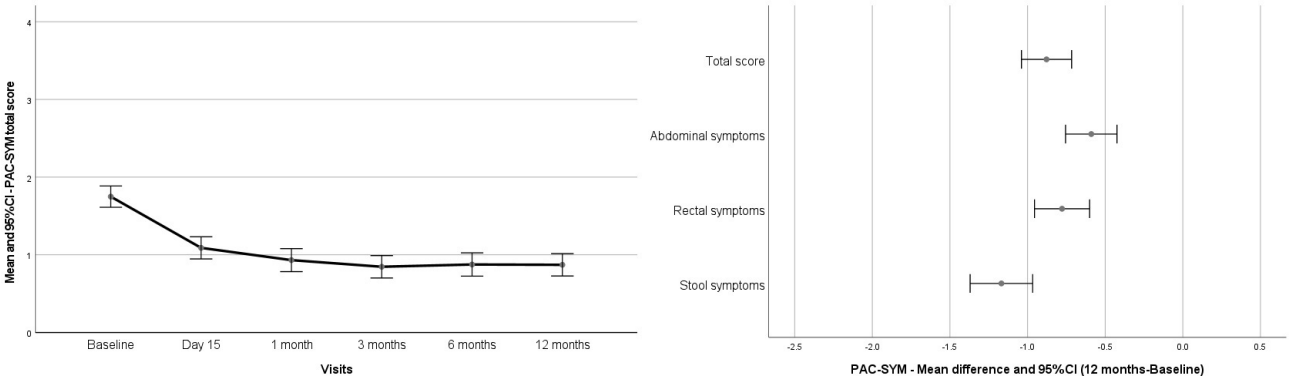

Figure 3 Patient assessment of constipation symptoms (PAC-SYM) questionnaire evolution from baseline to month 12 of follow-up.

The starting dose of naloxegol was 25 mg/day in 88.1% (n=111) and 12.5 mg/day in 11.1% (n=14) and one patient with 6.25 mg/day. The naloxegol dose was maintained unchanged during the study in 98.4% (124), only temporarily suspended in four patients due to adverse reactions. In one patient, the naloxegol dose was reduced and in two patients the initial dose was increased.

During the study, 48.4% of the patients (n=61) received concomitant treatment with laxatives. Of them 7.9% (10) were treated with concomitant laxatives for less than 3 months after the study initiation, and the remaining patients continued with laxatives during the study. Only nine patients (7.1%) needed rescue laxatives. The laxatives were lactulose (39.4%), macrogol (26.8%) and bisacodyl (9.9%), with doses according to each product specifications.

At baseline, a total of 77 patients (61.1%) were receiving chemotherapy and 107 (84.9%) were in treatment with other drugs that could cause constipation and unchanged during the study.

Evolution of symptoms and Karnofsky performance status

It was observed a statistically significant increase in the mean number of days a week with complete SBM from baseline (p<0.0001) at all the study visits (figure 4). The stool consistence (Bristol score) improved significantly versus baseline over time (p<0.0001).

Karnofsky performance status mean score was unchanged from baseline in patients still alive at each time point with value of 77.4% (95% CI 73.8% to 81.1%) at month 12.

There was a significant decrease in pain intensity between baseline and the next visits (p<0.001), allowing the maintenance of the scores under four points indicating an appropriate pain control during the study (figure 5).

Health-related QOL

No significant changes were shown in the EuroQoL-5D-5L dimensions and global health score from baseline to 6 and 12 months, with values for VAS of 56.1 mm (95% CI 52.8 to 59.6) at baseline, 58.5 mm (95% CI 54.8 to 62.1) at month six (p=0.471) and 59.2 mm (95% CI 55.4 to 63) at month 12 (p=0.236).

Adverse reactions to naloxegol

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

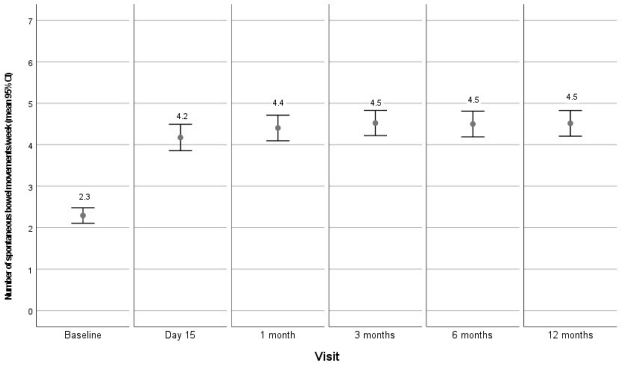

Figure 4 Evolution of stool movements from baseline to month 12 in the per-protocol population.

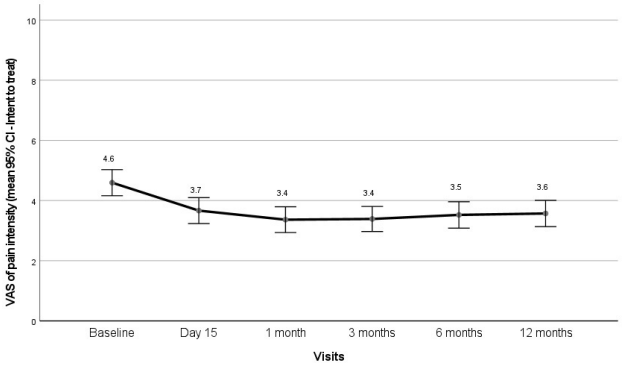

Figure 5 Visual Analogue Scale (VAS) of pain intensity.

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.

In figure 6, the flow diagram of patients reaching each follow-up visit is described.

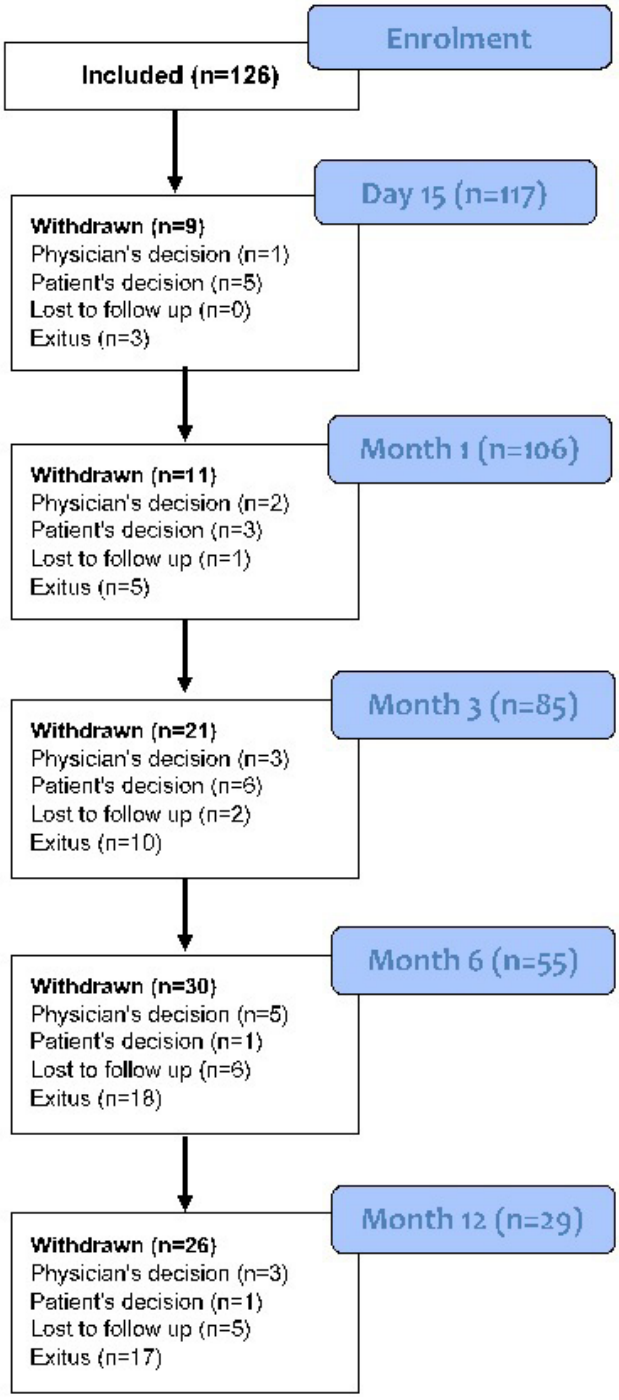

Figure 6 CONSORT flow diagram. CONSORT, Consolidated Standards of Reporting Trials.

DISCUSSION

OIC is a very frequent symptom observed in patients with cancer treated with opioids. The use of opioids became necessary for the control of the chronic pain, mainly secondary to the cancer or their metastases, but also for the management of the breakthrough pain present in 39.9%–80.5% of patients with cancer.[30] This study is relevant as it is the first one analysing prospectively QoL, efficacy and safety of naloxegol in patients with cancer on long-term treatment and in a real-world setting, since to date only data from case reports or small retrospective series have been published.[22 31–33] For the administration of naloxegol in the study, LIR was required, so it means that dietary and hygiene measures and laxatives failed to solve OIC before the study situation described in previous studies for up to 54% of patients[34]

From the observation of the 126 patients, we found clinically and statistically significant improvements in the constipation-related QOL and constipation symptoms measured by specific instruments for constipation, PAC-QOL (figure 1) and PAC-SYM (figure 3), respectively. These significant improvements started soon after the initiation of the treatment with naloxegol (day 15) and were maintained for 1 year. It is also relevant to outline that 58.7% of the patients maintained clinically significant improvements in PAC-QOL and 65.9% in PAC-SYM total scores at month 12. In the clinical trials with naloxegol, significant differences were only found in the PAC-QOL patient satisfaction subscale compared with placebo at 12 weeks versus baseline, with no significant differences in the other subscales.[35] The evolution proved significant for all the questionnaire subscales, although no control group was included in this observational study for comparisons (figure 1). It is relevant to note the significant correlation between the number of SBM and the improvements in PAC-SYM, PAC-QOL demonstrated in previous studies, and also observed in our experience, as a predictor of improvement in OIC symptoms and outcome.[36]

The response rate was high from the first visit at day 15 (71.4%) to month 12 (77.8%) with no statistically significant improvements between periods. No significant differences related to the dose nor to the use of concomitant laxatives during the study were shown (figure 2). For patients treated with doses of 25 mg of naloxegol, a slight but not significantly better response rate for patients on concomitant laxatives can be

observed. This fact can be explained by the percentage of patients with constipation previous to the initiation of treatment with opioids (27.8%), and the proportion of patients on treatment with other drugs that could induce constipation (84.9%), both situations needing to be treated with laxatives with other mechanisms of action.

The results of the two pivotal phase III trials (Kodiac 4 and Kodiac 5), double-blind, placebo-controlled studies with naloxegol for 12 weeks, in 1325 non-cancer patients, where concomitant laxative use was not permitted, in the pooled patients with LIR (54%), the response rate at 12 weeks was 42.5% for the 12.5 mg dose (n=240) and 47.7% (n=241) for the patients receiving 25 mg of naloxegol.[35 37] Compared with our study, at the same time-point, the response rate was 85.7% (95% CI 42.1% to 99.6%) at 12.5 mg and 72.4% (95% CI 59.1% to 83.3%) with 25 mg of naloxegol, considering the same criteria, without concomitant laxatives (figure 2). So, at 12 weeks, our results were similar for the 12.5 mg dose, but significantly better for the dose of 25 mg ($p<0.05$) in the patients with cancer of our study, compared with the results in clinical trials in patients without cancer. Since the number of patients, particularly in the lower naloxegol dose group was small, and no control group was included the results should be considered with caution. As no long-term studies are available with other peripherally acting μ-opioid receptor antagonists in patients with cancer, it was not possible to compare the efficacy results at this point.

The most common safety problems of naloxegol were gastrointestinal disorders, with a frequency of >5% (abdominal pain, diarrhoea, flatulence, nausea), as described in four phase III trials, one of which lasted 52 weeks.[38] These adverse events occurred mainly in the first 7 days of treatment. The safety profile observed in our study is consistent with the safety description of naloxegol, most events occurring in the first 15 days of treatment (67.9%), perhaps related to the restoration of the gastrointestinal movements, with low rate of discontinuation due to adverse effects (6/126) and considering that three of them were on concomitant treatment with laxative, mainly with only one product. As detailed in table 1, 25% of patients had history of cardiovascular disease and this group of patients were excluded in the naloxegol clinical trials due to safety.[32–35] Nevertheless, no cardiac adverse reactions to naloxegol were notified during the study.

As a measure of the patient's outcome, the global health-related QOL was assessed by means of the EuroQoL-5D-5L questionnaire. The results showed that the global health was maintained from baseline to month 12, which despite this condition, usually deteriorate over time in patients with cancer. The improvement in patient satisfaction dimension of PAC-QOL was also notorious, being near threefold greater than improvement in the other subscales (figure 1), perhaps due to the adequate symptom relief and the good tolerability to naloxegol.

The analgesic response was maintained throughout follow-up (figure 5), and no patients withdrew from the study due to the opioid suspension, so one of the main problems associated with opioid therapy, that results in opioid rotation or discontinuation as a result of OIC with an inadequate response, was not observed in the study. Naloxegol has demonstrated in previous studies, similar efficacy in treating OIC independently of maintenance opioid type, dose, or duration of opioid use at baseline, although these data have not been explored in our analysis, neither the need for changes in opioid doses or opioid rotation for pain control.[37 39 40] We must add that there were no significant baseline characteristics related to better or worse efficacy of naloxegol in patients with OIC and cancer (online resource 1).

The limitations of our study are related to its observational design. There was no control group, so the findings should be confirmed in randomised and controlled clinical trials, in particular compared with other products for the treatment of OIC, or to measure the placebo effect. The reported data derive from the intent-to-treat population analyses where the efficacy findings may be underestimated, as can be observed in the interim analyses of the study already published and from the sensitivity analysis performed.[23] The number and causes of drop-out are comparable to the figures observed in other long-term studies, but due to the final drop-out including patients who die, the treatment of the missing data could narrow the confidence intervals for the main objective variable.[38]

Based on the results obtained in this first long-term and real-world-data study in patients with cancer and OIC, we contributed with data about the sustained efficacy and safety of naloxegol for the treatment of OIC in this group of patients.

Author affiliations
[1]Medical Oncology Department, Hospital Regional Universitario de Málaga, Málaga, Spain
[2]IBIMA, Málaga, Spain
[3]Medical Oncology Department, Complejo Hospitalario Virgen de la Macarena, Sevilla, Spain
[4]Medical Oncology Department, Hospital Universitario de Torrejón, Torrejón de Ardoz, Madrid, Spain
[5]Radiation Oncology Department, Hospital Universitario de Gran Canaria Dr Negrin, Las Palmas de Gran Canaria, Spain
[6]Medical Oncology Department, Hospital Universitario San Cecilio, Granada, Spain
[7]Medical Oncology Department, Hospital Son Llatzer, Palma de Mallorca, Illes Balears, Spain
[8]Medical Oncology Department, COSAGA, Ourense, Spain
[9]Palliative Care Service, Institut Català d'Oncologia, L'Hospitalet de Llobregat, Barcelona, Spain
[10]Medical Oncology Department, Centro Oncológico de Galicia, La Coruña, Spain
[11]Medical Oncology Department, Hospital Universitario Infanta Cristina, Badajoz, Spain
[12]Radiation Oncology Department, Hospital Universitari Vall d'Hebron, Barcelona, Spain

[13]Palliative Care Department, Consorci Sanitari Terrassa, Terrassa, Barcelona, Spain
[14]Medical Oncology Department, Hospital Universitario de Donostia, San Sebastian, Guipúzcoa, Spain
[15]Medical Oncology Department, Hospital Universitario Reina Sofía, Córdoba, Spain
[16]Medical Oncology Department, Hospital General Universitario La Paz, Madrid, Spain
[17]Medical Oncology Department, Hospital Universitario Fundación Alcorcón, Alcorcón, Madrid, Spain
[18]Medical Department, Kyowa Kirin Farmacéutica S.L, Madrid, Spain
[19]Medical Department, E-C-BIO, S.L, Las Rozas, Madrid, Spain

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ORCID iDs
Manuel Cobo Dols http://orcid.org/0000-0003-3402-1144
Begoña Soler López http://orcid.org/0000-0001-5853-2307

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