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Randomised clinical trial: the long-term safety and tolerability of naloxegol in patients with pain and opioid-induced constipation

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SUMMARY

Background
Opioid-induced constipation (OIC) is a common adverse effect of opioid therapy.

Aim
To evaluate the long-term safety and tolerability of naloxegol, an oral, peripherally acting μ-opioid receptor antagonist (PAMORA), in patients with noncancer pain and OIC.

Methods
A 52-week, multicenter, open-label, randomised, parallel-group phase 3 study was conducted in out-patients taking 30–1000 morphine-equivalent units per day for ≥4 weeks. Patients were randomised 2:1 to receive naloxegol 25 mg/day or usual-care (UC; investigator-chosen laxative regimen) treatment for OIC.

Results
The safety set comprised 804 patients (naloxegol, n = 534; UC, n = 270). Mean exposure duration was 268 days with naloxegol and 297 days with UC. Frequency of adverse events (AEs) was 81.8% with naloxegol and 72.2% with UC. Treatment-emergent AEs occurring more frequently for naloxegol vs. UC were abdominal pain (17.8% vs. 3.3%), diarrhoea (12.9% vs. 5.9%), nausea (9.4% vs. 4.1%), headache (9.0% vs. 4.8%), flatulence (6.9% vs. 1.1%) and upper abdominal pain (5.1% vs. 1.1%). Most naloxegol-emergent gastrointestinal AEs occurred early, resolving during or after naloxegol discontinuation and were mild or moderate in severity; 11 patients discontinued due to diarrhoea and nine patients owing to abdominal pain. Pain scores and mean daily opioid doses remained stable throughout the study; no attributable opioid withdrawal AEs were observed. Two patients in each group had an adjudicated major adverse cardiovascular event unrelated to study drug; no AEs were reported nor adjudicated as bowel perforations.

Conclusion
In patients with noncancer pain and opioid-induced constipation, naloxegol 25 mg/day up to 52 weeks was generally safe and well tolerated.

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INTRODUCTION

Opioid-induced constipation (OIC) is a very common adverse effect of opioid therapy[1, 2] and is considered by patients as the most bothersome.[1] Stimulation of μ-opioid receptors in the gastrointestinal (GI) tract leads to impaired GI transit and motility with decreased secretions, commonly leading to constipation.[2–4] Given the increase in prevalence of long-term use of opioid medications in patients with noncancer pain,[5] the management of OIC in this patient population has become a major therapeutic challenge.

Treatment of OIC typically employs conservative approaches, including increased fluid, fibre and exercise[2, 4] in conjunction with laxative use[2, 4, 6] to facilitate bowel movements (BMs). However, data on the usefulness of nonpharmacological strategies are limited.[7] Further, the use of laxatives as a treatment for OIC is hampered by a lack of placebo-controlled trials definitively demonstrating robust efficacy and tolerability.[8] Lubiprostone is a US Food and Drug Administration (FDA)-approved pharmacotherapy that acts via a non-opioid receptor mechanism to alleviate OIC in patients with noncancer pain.[9] Lubiprostone works by activation of chloride channels in the intestine to facilitate stool movement.[9] Although methylnaltrexone is also an FDA-approved option for the treatment of OIC, this agent is only available as a subcutaneous formulation and is exclusively indicated for patients with advanced medical illness.[6]

Naloxegol is a novel, oral, peripherally acting μ-opioid receptor antagonist (PAMORA) in clinical development as a targeted therapy for treatment of the underlying cause of OIC. Naloxegol is a PEGylated derivative of naloxone, a μ-opioid receptor antagonist. PEGylation confers increased oral bioavailability and peripheral selectivity to the naloxone moiety by a reduction in passive permeability across the blood-brain barrier. Naloxegol is also a substrate of the P-glycoprotein (PGP) transporter, which promotes efflux of naloxegol and serves to further restrict its entry into the central nervous system. The efficacy of naloxegol in patients with OIC and noncancer pain was demonstrated in two replicate double-blind, randomised, placebo-controlled phase 3 trials, each over 12 weeks.[10] In both studies, naloxegol 25 mg was associated with statistically significant improvements in stool frequency and numerical improvements in OIC symptoms compared with placebo, as assessed by response rate in the overall population over 12 weeks and in a subgroup of patients with inadequate response to laxatives. Furthermore, naloxegol 25 mg significantly improved time to first post-dose spontaneous bowel movement (SBM), and days per week with an SBM (end point defined to assess regularity).

The primary objective of this study was to evaluate the long-term safety and tolerability of naloxegol 25 mg in patients with OIC and noncancer pain. The secondary objective was to compare the long-term safety and tolerability of naloxegol 25 mg to that of an investigator-managed regimen of laxatives (usual care).

METHODS

Study design and patients

This was a phase 3, 52-week, multicentre, open-label, randomised, parallel-group, safety and tolerability study (KODIAC-08, NCT01336205), conducted from April 18, 2011, to December 3, 2012, in the US. Eligible patients aged ≥18 to <85 years were enrolled as new patients without prior naloxegol treatment after screening and confirmation of OIC, or as rollover patients from either the 12-week KODIAC-05 study (NCT01323790) or the 3-month safety extension of the 12-week KODIAC-04 study (NCT01395524). All patients were receiving a stable maintenance opioid therapy at a dose of 30–1000 morphine-equivalent units (MEUs) per day for noncancer pain. Before randomisation (in the parent study for rollover patients), OIC was confirmed over a 2-week period and defined as <3 SBMs per week on average with ≥1 of the following symptoms in ≥25% of BMs: Bristol stool scale stool type 1 or 2; moderate, severe or very severe straining; or incomplete BM. Patients who had 0 BMs or an uneven distribution of SBMs (0 SBMs in 1 week with ≥4 SBMs in the other week) over the 2-week OIC confirmation period were not randomised. During confirmation of OIC, laxative use (other than rescue medication) was not permitted.

Exclusion criteria included conditions associated with diarrhoea, intermittent loose stools, or constipation not related to opioid use that could confound the interpretation of results; conditions associated with potential impairment of the structural integrity of the GI tract, including surgery on the colon or abdomen within 60 days of screening; acute GI conditions imposing risk to the patient (e.g. acute faecal impaction/complete obstipation, acute surgical abdomen, suspicious abdominal or rectal examination results) or inadequate response to laxative rescue during OIC confirmation; treatment with opioids for cancer-related pain, or history of cancer within 5 years of screening (except for basal cell or

squamous cell skin cancer); conditions associated with increased permeability of the blood-brain barrier (e.g. multiple sclerosis); increased risk for ventricular arrhythmia; use of mixed opioid agonist/antagonists, opioid antagonists, or products containing naloxone or naltrexone; and use of strong cytochrome P450 3A4 or PGP inhibitors. Laxatives were prohibited for patients in the naloxegol arm. However, use of bisacodyl as a rescue medication (10–15 mg for a total of three doses separated by 12-h intervals) was permitted when 72 h had passed without a BM.

Patients were randomised 2:1 to open-label naloxegol 25 mg once daily or usual-care treatment, using an internal computer-generated randomisation scheme. In patients receiving usual care, the treatment regimen was selected and prescribed as the investigator would typically do and in accordance with his or her clinical experience, using laxatives available for use in constipation or OIC, including those that the patient may already have been using prior to the study. Patients randomised to usual-care treatment were not permitted to use any medication for their constipation other than the investigator-approved medication; any change in laxatives required the prior agreement of the investigator. Usual-care treatment consisted of a laxative regimen chosen by the investigator from a broad range of laxatives; however, peripheral μ-opioid antagonists such as methylnaltrexone or naloxone-containing products were not permitted. The treatment regimen could be modified by the investigator at any point during the 52-week study period. Lastly, no specific rescue protocol was determined for patients randomised to receive usual care. Patients randomised to naloxegol were required to stop all other laxatives or bowel regimens during the treatment period but were permitted to use the rescue medication bisacodyl as previously described.

This study was performed in accordance with the Declaration of Helsinki and the International Conference on Harmonisation (ICH)/Good Clinical Practice, applicable regulatory requirements, and the AstraZeneca policy on Bioethics. The study protocol and informed consent form was approved by an ethics committee/institutional review board. All patients provided written informed consent before any study procedures were conducted.

Assessments

Safety and tolerability were assessed by the incidence, nature, intensity and relatedness to treatment of all adverse events (AEs); AEs leading to study discontinuation; AEs of special interest; and significant changes in health status as determined by laboratory and clinical assessments, vital signs, electrocardiograms (ECGs) and physical examination. AEs were collated by investigator query and patient self-report, and recorded by the investigator using electronic case report forms at the OIC confirmation visit, baseline, weeks 1 and 2 of treatment, every month up to 12 months, and at the follow-up visit (2 weeks after the month 12 visit). Vital signs and laboratory, clinical, and ECG assessments were performed at screening, baseline, weeks 1 and 2, months 1, 3, 6, 9, 12, and follow-up. Physical examinations were conducted at screening, baseline and months 6 and 12. Treatment-emergent AEs were defined as those occurring during the treatment period. AEs of special interest included selected cardiovascular events [major adverse cardiovascular events (MACE, defined as cardiovascular death, myocardial infarction, stroke), congestive heart failure], AEs with a potential relationship to blood pressure changes or opioid withdrawal, and serious GI events adjudicated for bowel perforation. Serious GI AEs and cardiovascular AEs were independently and prospectively adjudicated by separate external committees to identify any cases of bowel perforation or MACE, respectively.

The effect of treatment on opioid requirements and pain management was assessed by the following: change from baseline in the mean daily opioid dose from randomisation to month 1, months 1 to 3, months 3 to 6, months 6 to 9 and months 9 to 12; change from baseline in the Numeric Rating Scale (NRS) for pain (0 = no pain; 10 = worst possible pain)[11] for weeks 1 and 2 and months 1, 2, 3, 6, 9 and 12; and observed values and change from baseline in composite score of the modified Himmelsbach Opioid Withdrawal Scale (mHOWS)[12, 13] to assess centrally mediated opioid withdrawal symptoms at 2 h following the first dose, week 1, and months 1, 3, 6, 9 and 12. The mHOWS rates yawning, lacrimation, rhinorrhea, perspiration, tremor, mydriasis, piloerection and restlessness on a scale from 0 (none) to 3 (severe).[12] Patients were asked to rate their average pain over the past week on the NRS at study visits. In addition, the mean bisacodyl dose per week for naloxegol-treated patients was assessed from randomisation to month 1, months 1 to 3, months 3 to 6, months 6 to 9 and months 9 to 12.

Analysis

Baseline data for patients recruited from previous studies were summarised as of entry into those studies. Safety analysis was performed using descriptive statistics and was based on the safety-analysis set (randomised patients who received ≥1 dose of study drug or usual care). A

formal calculation of sample size was not performed. Determination of sample size was based on ICH exposure requirements,[14] with the goal of having ≥300 and ≥100 patients complete 6 and 12 months of exposure, respectively. Randomisation of patients was adjusted as necessary to meet these requirements.

RESULTS

Demographical and disease characteristics

Of the 844 patients who were randomised, 760 (90%) were new patients and 84 (10%) participated in previous naloxegol studies (i.e. rollover patients; Figure 1). The safety-analysis set consisted of 534 patients in the naloxegol 25-mg arm and 270 patients in the usual-care arm. Completion rates were 58.1% in the naloxegol group and 67.3% in the usual-care group.

Patients were predominantly white, with a mean age of 52.7 years (Table 1). Pain history and baseline total daily opioid dose and history were similar between treatment groups for newly randomised patients (Table 2).

Use of maintenance opioid medications in patients from the safety-analysis set is summarised in Table 3. Distribution of maintenance opioid medications was similar between treatment groups. The most commonly used opioid medications were hydrocodone + acetaminophen (32.3%), morphine (27.9%), oxycodone (25.0%), oxycodone + acetaminophen (18.9%) and tramadol (13.6%). Use of breakthrough opioid medications (those taken by the patient from treatment initiation to study completion or discontinuation) was also assessed. Overall usage of breakthrough opioid medications was balanced between treatment groups (naloxegol, 36.0%; usual care, 34.8%). The most commonly used breakthrough medications were hydrocodone + acetaminophen (9.8%), oxycodone (9.6%) and oxycodone + acetaminophen (8.0%).

In the 2 weeks before screening, 66.8% of patients had taken a laxative. The laxative classes used were balanced between the treatment groups, with stimulants (54.4%), stool softeners (30.5%) and polyethylene glycol (14.7%) as the most commonly used laxatives. Most patients (72.4%) were taking only one laxative class before screening.

At the start of the study, musculoskeletal and connective tissue disorders were present in 87.4% of patients and primarily consisted of back pain (52.9%), osteoarthritis (23.3%) and muscle spasms (17.2%). Psychiatric disorders were also prevalent, occurring in 60.9% of patients, with insomnia (34.7%), depression (34.2%) and

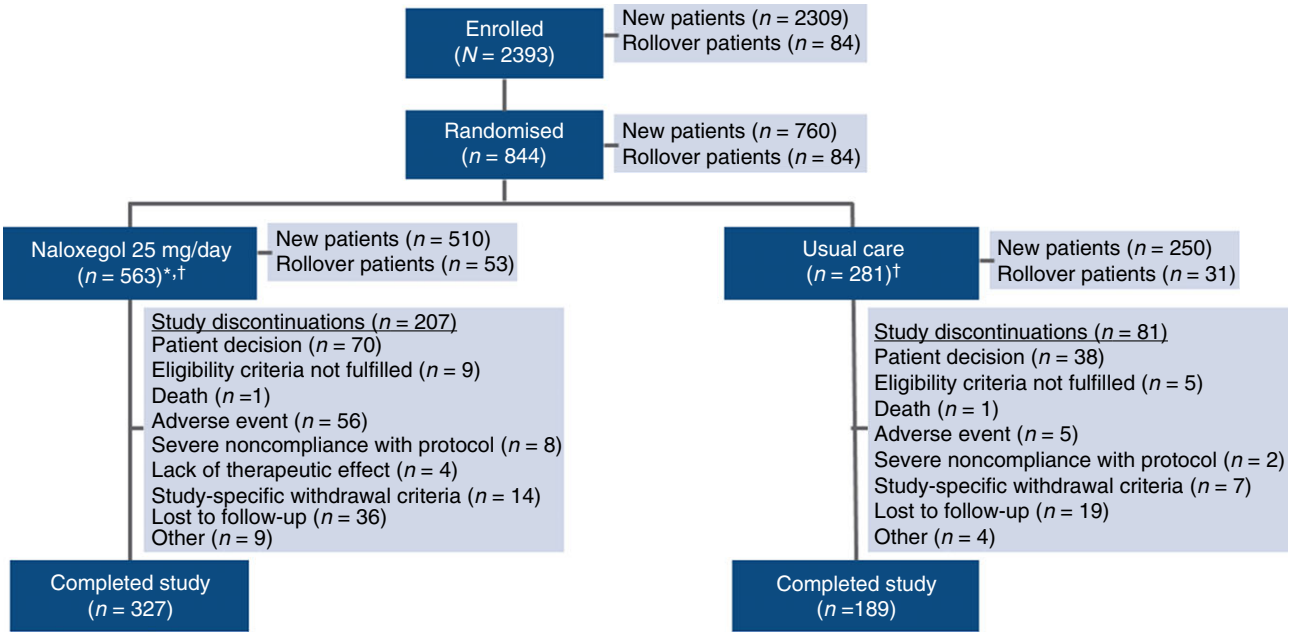

Figure 1 | Patient disposition. *Four patients randomised to naloxegol did not receive study treatment because of patient decision (n = 2) and did not fulfill eligibility criteria (n = 2). †Thirty-six patients (naloxegol 25 mg, n = 25; usual care, n = 11) who previously or concurrently participated in the naloxegol programme at another study centre or randomised at two sites where data integrity issues were identified were excluded from the safety-analysis set and were not included in the numbers of patients completing or discontinuing the study.

Table 1 | Patient baseline characteristics (safety-analysis set)*

Characteristic	Naloxegol 25 mg (*n* = 534)	Usual care (*n* = 270)
Mean (s.d.) age (years)	52.8 (10.1)	52.7 (10.2)
Age category, *n* (%)		
<50 years	179 (33.5)	96 (35.6)
≥50 to <65 years	302 (56.6)	137 (50.7)
≥65 years	53 (9.9)	37 (13.7)
Women, *n* (%)	353 (66.1)	179 (66.3)
Race, *n* (%)		
White	423 (79.2)	204 (75.6)
Black	98 (18.4)	60 (22.2)
Asian	4 (0.7)	3 (1.1)
American Indian or Alaska Native	4 (0.7)	1 (0.4)
Other	5 (0.9)	2 (0.7)

* Data for rollover patients were pre-treatment values from the respective pivotal 12-week studies (KODIAC-04 and KODIAC-05).

Table 2 | Pain history and baseline opioid use (new patients)

Characteristic	Naloxegol 25 mg (*n* = 481)	Usual care (*n* = 240)
Primary reason for pain, *n* (%)*		
Back pain	272 (56.5)	131 (54.6)
Arthritis	39 (8.1)	22 (9.2)
Fibromyalgia	33 (6.9)	14 (5.8)
Joint pain	20 (4.2)	15 (6.3)
Other†	117 (24.3)	57 (23.8)
Mean (s.d.) opioid use		
Duration of current use, months	47.8 (49.1)	49.5 (53.3)
Lifetime use (months)	101.0 (89.3)	102.3 (86.0)
Daily dose (mg/day)	151.5 (253.8)	136.7 (138.5)

* Percentage data based on the number of patients in the safety-analysis set in each treatment group and patient group.

† Includes headache/migraine, neuralgia, pain syndrome and other conditions such as localised musculoskeletal pain.

Table 3 | Maintenance opioid medications during treatment (safety-analysis set)*

Opioid Class/Drug, *n* (%)†	Naloxegol 25 mg (*n* = 534)	Usual care (*n* = 270)
Natural opium alkaloids	482 (90.3)	247 (91.5)
Hydrocodone + acetaminophen	176 (33.0)	84 (31.1)
Morphine	157 (29.4)	67 (24.8)
Oxycodone	126 (23.6)	75 (27.8)
Oxycodone + acetaminophen	101 (18.9)	51 (18.9)
Hydromorphone	26 (4.9)	21 (7.8)
Hydrocodone	25 (4.7)	18 (6.7)
Oxymorphone	20 (3.7)	15 (5.6)
Codeine + acetaminophen	8 (1.5)	2 (0.7)
Codeine	0	2 (0.7)
Butalbital + codeine	1 (0.2)	0
Other opioids	77 (14.4)	45 (16.7)
Tramadol	68 (12.7)	41 (15.2)
Tapentadol	7 (1.3)	4 (1.5)
Acetaminophen + tramadol	3 (0.6)	0
Phenylpiperidine derivatives	52 (9.7)	26 (9.6)
Fentanyl	50 (9.4)	26 (9.6)
Pethidine	2 (0.4)	0

* Data for rollover patients were summarised as of entry into the respective pivotal 12-week studies (KODIAC-04 and KODIAC-05).

† Use of methadone, partial opioid agonists and opioid agonist/antagonists was prohibited and was recorded as a protocol deviation when appropriate. Within each treatment group, use of methadone, buprenorphine or naloxone + pentazocine was <1%.

anxiety (27.0%) being the most common conditions. Gastroesophageal reflux disease was reported by 29.5% of patients. Primary reasons for pain were back pain (55.9%), 'other' (21.1%, mainly localised musculoskeletal pain) and arthritis (8.5%). Nearly all patients (98.3%) were taking other medications (in addition to opioids) during treatment. Benzodiazepine derivatives (41.4%), other antidepressants (31.1%) and 3-hydroxy-3-methyl-glutaryl coenzyme A reductase inhibitors (30.5%) were the most commonly used medication classes. Medications used by ≥10% of patients were gabapentin (20.5%), ibuprofen (16.8%), aspirin (15.3%), alprazolam (15.3%), lisinopril (15.2%), omeprazole (14.9%), simvastatin (14.6%), vitamins (13.1%), duloxetine hydrochloride (12.6%), carisoprodol (12.1%), zolpidem tartrate (10.4%) and hydrochlorothiazide (10.2%).

Exposure to medication

Mean (s.d.) duration of exposure was 268.1 (136.5) days with naloxegol and 296.7 (120.8) days with usual care. In the usual-care arm, 213 (79%) patients took laxatives at the start of the study, and 197 (73%) did not change their laxative medication during the study, including 25 (9%) patients who did not start or take any laxative medication. Laxatives used in >10% of usual-care patients were bisacodyl (*n* = 102, 38%), macrogol (*n* = 38, 14.1%) and docusate sodium (*n* = 27, 10%).

Adverse events

A majority of patients in each group had a treatment-emergent AE; abdominal pain, diarrhoea, nausea, headache, flatulence, bronchitis and upper abdominal pain occurred more frequently with naloxegol than usual care (Table 4). The incidence of serious AEs (SAEs) was similar between groups.

Two deaths occurred during the study. One death occurred in a patient treated with naloxegol; this individual experienced an SAE of idiopathic generalised epilepsy 20 days after discontinuation of study drug. The second death occurred during treatment in a patient in the usual-care group who had taken naloxegol 12.5 mg in a previous study. The last dose of naloxegol was taken at 96 days prior to death. This patient died in her sleep from an unknown cause on day 95 of this study. Neither death was considered to be related to study medication.

Table 4 | Adverse event summary (safety-analysis set)

Adverse event, *n* (%)*	Naloxegol 25 mg (*n* = 534)	Usual care (*n* = 270)
Any AE†	437 (81.8)	195 (72.2)
Serious AE	51 (9.6)	30 (11.1)
AE leading to discontinuation of IP	56 (10.5)	NA‡
Death	1 (0.2)	1 (0.4)
Treatment-emergent AEs (≥5% in any treatment group)§		
Abdominal pain	95 (17.8)	9 (3.3)
Diarrhoea	69 (12.9)	16 (5.9)
Nausea	50 (9.4)	11 (4.1)
Back pain	48 (9.0)	24 (8.9)
Headache	48 (9.0)	13 (4.8)
Flatulence	37 (6.9)	3 (1.1)
Arthralgia	33 (6.2)	16 (5.9)
Nasopharyngitis	33 (6.2)	15 (5.6)
Upper respiratory tract infection	31 (5.8)	23 (8.5)
Bronchitis	30 (5.6)	12 (4.4)
Vomiting	27 (5.1)	15 (5.6)
Upper abdominal pain	27 (5.1)	3 (1.1)
Sinusitis	23 (4.3)	19 (7.0)
Urinary tract infection	22 (4.1)	22 (8.1)

AE, adverse event; IP, investigational product; NA, not applicable.

* Percentage data based on the number of patients in the safety-analysis set in each treatment group and patient group.

† Occurring during either the treatment or post-treatment follow-up periods.

‡ Not assessed because usual care was not considered an IP.

§ Occurring during the treatment period.

Adverse events leading to study discontinuation

Adverse events leading to discontinuation of investigational product (IP) occurred in 56 (10.5%) patients in the naloxegol group; the most common associated preferred terms were diarrhoea (*n* = 11, 2.1%), abdominal pain (*n* = 9, 1.7%) and vomiting (*n* = 5, 0.9%). By definition, patients receiving usual care were not administered an IP and therefore could not discontinue IP due to AEs; 5 (1.8%) of patients in this group withdrew from the study due to AEs.

Treatment-emergent GI AEs

Most GI AEs were mild or moderate in intensity, occurred in the first 12 weeks of treatment, and resolved during treatment or after discontinuation of treatment. Abdominal pain was the most commonly reported AE with naloxegol treatment (Table 4); severity was mild in 53 (9.9%) patients, moderate in 30 (5.6%) and severe in 12 (2.2%) patients. In the usual-care group, severity of abdominal pain reported as an AE was mild in two (0.7%) patients, moderate in four (1.5%) and severe in three (1.1%).

Of the patients treated with naloxegol who reported abdominal pain, the majority had onset within the first week (59 of 95) and had a total AE duration of ≤14 days (55 of 95). Onset in the usual-care group varied over the treatment period, with none starting during the first week of treatment. Abdominal pain was reported as a SAE by one patient who was treated with naloxegol. The event occurred on day 19 of treatment, was severe in intensity and unrelated to study treatment, but resolved by day 22 of treatment and did not lead to discontinuation. The patient required treatment (not specified by the investigator) and subsequently recovered. Nine patients with abdominal pain discontinued treatment with naloxegol.

Adverse events of special interest

Adverse events pre-specified as being of special interest included selected cardiovascular events (i.e. MACE events, congestive heart failure), AEs potentially related to changes in blood pressure or opioid withdrawal, and GI SAEs adjudicated for bowel perforation.

Adverse events determined by independent adjudication to meet diagnostic criteria for a MACE event occurred in two patients in each treatment group, including the two deaths described previously that occurred during the study; neither of which were considered to be related to study medication. Any unexplained death as per adjudication charter was automatically

assigned as a MACE event. In addition, one patient in the usual-care group had an SAE of ischaemic cerebral infarction on day 74, which was adjudicated as a cerebrovascular accident. A patient in the naloxegol group had an SAE of increased troponin on day 156, which was detected upon admission to hospital for symptoms of altered consciousness, twitching and confusion. Elevations of troponin, potassium, creatine phosphokinase and liver transaminases were noted upon admission; serial ECG was performed and troponin levels were monitored. The patient was treated for hyperkalemia, recovered and was subsequently discharged. The preliminary diagnosis was non-ST elevated myocardial infarction, with a final diagnosis of elevated troponin. The event of elevated troponin was adjudicated as acute myocardial infarction and resulted in discontinuation from the study. Both events were considered unrelated to study drug.

The number of patients with AEs related to decreased blood pressure/orthostatic hypotension was five (0.9%) for the naloxegol group and 5 (1.9%) for the usual-care group; AEs related to increases in blood pressure were reported in 21 (3.9%) naloxegol-treated patients and 12 (4.4%) patients receiving usual care. Three patients (0.6%) receiving naloxegol reported an AE of syncope, and none of the events were considered related to treatment.

Few GI SAEs were reported [naloxegol, $n = 3$ (0.6%); usual care, $n = 3$ (1.1%)]. No GI SAEs were adjudicated as bowel perforations.

Adverse events reported as opioid withdrawal AEs during the treatment period occurred in two patients taking naloxegol and none in the usual-care arm; both events were attributed to a change in opioid dose. The first event was reported in a patient receiving twice-daily administration of morphine 60 mg that was tapered to a dose of 30 mg. The second event occurred in a patient at 2 weeks after running out of medication (20 mg oxycodone/acetaminophen twice daily). An additional patient administered naloxegol experienced mild opioid withdrawal during the follow-up period. The event occurred 3 days after completion of study medication, resolved 12 days later and was considered possibly related to treatment. Most patients did not have a change from baseline in mHOWS during the study. At 2 h after the first dose on day 1, an increase in mHOWS score of ≥3 was observed in three patients (0.6%) in the naloxegol group and one patient (0.4%) in the usual-care group. Twenty-three patients (4.3%) in the naloxegol group and 10 (3.8%) in the usual-care group recorded a maximum change from baseline of ≥3 in the mHOWS score during treatment. Hyperhidrosis was reported in 17 patients (3.2%) treated with naloxegol vs. one patient (0.4%) in the usual-care group.

Pain scores were similar between patients receiving naloxegol or usual care and were stable throughout the study, with a mean change from baseline of ≤0.4 for either treatment group. Mean daily opioid doses remained stable throughout the study (at randomisation to month 1, months 1 to 3, months 3 to 6, months 6 to 9 and months 9 to 12) for new patients, with a mean change from baseline ranging from −1.2 to −5.7 MEUs for the naloxegol group and −2.7 to −5.3 MEUs for the usual-care group; findings were similar in rollover patients.

Rescue medication use

During treatment with naloxegol, use of bisacodyl rescue medication was minimal, with median doses per week of 1.1 mg from randomisation to month 1, and 0 mg from months 1 to 3, months 3 to 6, months 6 to 9 and months 9 to 12. Rescue medication was not captured for the usual-care treatment group, as this was considered part of the usual-care treatment regimen.

DISCUSSION

In patients with noncancer pain and OIC, naloxegol 25 mg was generally safe and well tolerated over 52 weeks. The overall safety and tolerability data were consistent with the findings from the phase 3 placebo-controlled studies, which were conducted over a 12-week period. The observed AE rate of 81.8% for naloxegol 25 mg in the current study was higher than the rates observed in the two phase three studies (KODIAC-04, 61.2%; KODIAC-05, 69.0%), consistent with a longer treatment duration.[10] Although SAEs for naloxegol 25 mg were lower in the 12-week phase 3 studies (KODIAC-04, 3.3%; KODIAC-05, 3.4%),[10] rates for naloxegol 25 mg vs. usual-care treatment in the current 52-week study were similar (Table 4) and were <3% across system organ classes. Comparable rates of AEs leading to discontinuation of naloxegol 25 mg were observed across the 12-week (10.3% for both KODIAC-04 and KODIAC-05)[10] and 52-week (Table 4) studies. In addition, pain scores and mean daily opioid doses in the naloxegol and usual-care groups were stable and comparable throughout the study, and there were no attributable opioid withdrawal AEs observed in either treatment arm.

Further, no new safety findings emerged with continued naloxegol treatment beyond 12 weeks. The

occurrence of abdominal pain (17.8%), the most frequently reported AE, was comparable to that reported in the 12-week phase 3 studies (KODIAC-04, 12.6%; KODIAC-05, 19.0%).[10] Of particular note are the comparable rates of MACE events and AEs related to blood pressure changes between usual care and naloxegol. No events were adjudicated as bowel perforations. In addition, long-term use of naloxegol was not associated with significant changes in opioid dosing requirements or pain and withdrawal scores.[10]

There is little published information on the long-term safety of peripheral opioid receptor antagonists with continued administration in the treatment of OIC. Methylnaltrexone was examined in a 3-month open-label extension study of patients with advanced illness and OIC.[15] Methylnaltrexone was administered on an as needed basis, starting with a dose of 0.15 mg/kg given subcutaneously and the option to increase the dose to 0.30 mg/kg if a BM failed to occur within 4 h, or to decrease the dose to 0.075 mg/kg if drug-related AEs occurred. Apart from AEs related to the medical status of the patient population, reported AEs were primarily GI in nature and consisted of abdominal pain (30.5%), nausea (20.7%), vomiting (19.5%) and flatulence (12.2%). Similarly, pain scores were unaltered and opioid withdrawal was not observed as a result of treatment with methylnaltrexone.

Strengths of this study include the use of a 2-week period for confirmation of OIC before randomisation, which ensured that all randomised patients were experiencing active OIC at the start of treatment. Also, the inclusion of an investigator-managed laxative regimen for patients in the usual-care control group approximates real-world practice for the management of OIC and allows for assessment of baseline rates of AEs resulting from OIC-targeted therapy.

There are several limitations of this study. The open-label study design allowed patients to know their treatment group assignment and patients were informed of potential risks with naloxegol treatment during the informed consent procedure; however, potential risks of usual-care treatments were not included in informed consent, thereby introducing a potential confounding bias in the reporting of AEs and the decision to continue in the study. Because an investigator-managed laxative regimen (with a variety of laxative options) was administered to patients in the usual-care group, the treatment regimen would be slightly different for each patient and would likely impact the type, number and severity of the individual AEs reported by these patients. In addition, patients receiving usual care were allowed to change their treatment rather than having to discontinue the study for AEs. Thus, it is likely that AEs were underrepresented in the usual-care group and overrepresented in the naloxegol group, as compared to what might be observed in a real-world clinical setting. Lastly, the absence of a blinded placebo group does not enable direct comparison of naloxegol or usual care to no treatment.

In conclusion, long-term administration of naloxegol 25 mg was generally safe and well tolerated, with preservation of opioid analgesia in patients with noncancer pain and OIC. The most common AEs observed in the naloxegol group were GI, as would be expected based on the underlying mechanism of action at enteric μ-opioid receptors. Treatment with naloxegol is a viable option for the management of OIC in this patient population (ClinicalTrials.gov registration: NCT01336205).

AUTHORSHIP

Guarantor of the article: Dr Lynn Webster.

Author contributions: The study protocols were designed by AstraZeneca LP with input from the academic authors, who served as consultants to the sponsor. Study conduct, monitoring and data analysis was performed by Quintiles, a contract research organisation, under the supervision of the sponsor. All authors had full access to the study data and attest to the completeness and accuracy of the data. All authors reviewed and revised all versions of the manuscript, and approved the final version of the manuscript.

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