

## ORIGINAL ARTICLE

# Naloxegol for Opioid-Induced Constipation in Patients with Noncancer Pain

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## ABSTRACT

**BACKGROUND**

Opioid-induced constipation is common and debilitating. We investigated the efficacy and safety of naloxegol, an oral, peripherally acting,  $\mu$ -opioid receptor antagonist, for the treatment of opioid-induced constipation.

**METHODS**

In two identical phase 3, double-blind studies (study 04, 652 participants; study 05, 700 participants), outpatients with noncancer pain and opioid-induced constipation were randomly assigned to receive a daily dose of 12.5 or 25 mg of naloxegol or placebo. The primary end point was the 12-week response rate ( $\geq 3$  spontaneous bowel movements per week and an increase from baseline of  $\geq 1$  spontaneous bowel movements for  $\geq 9$  of 12 weeks and for  $\geq 3$  of the final 4 weeks) in the intention-to-treat population. The key secondary end points were the response rate in the subpopulation of patients with an inadequate response to laxatives before enrollment, time to first postdose spontaneous bowel movement, and mean number of days per week with one or more spontaneous bowel movements.

**RESULTS**

Response rates were significantly higher with 25 mg of naloxegol than with placebo (intention-to-treat population: study 04, 44.4% vs. 29.4%,  $P=0.001$ ; study 05, 39.7% vs. 29.3%,  $P=0.02$ ; patients with an inadequate response to laxatives: study 04, 48.7% vs. 28.8%,  $P=0.002$ ; study 05, 46.8% vs. 31.4%,  $P=0.01$ ); in study 04, response rates were also higher in the group treated with 12.5 mg of naloxegol (intention-to-treat population, 40.8% vs. 29.4%,  $P=0.02$ ; patients with an inadequate response to laxatives, 42.6% vs. 28.8%,  $P=0.03$ ). A shorter time to the first postdose spontaneous bowel movement and a higher mean number of days per week with one or more spontaneous bowel movements were observed with 25 mg of naloxegol versus placebo in both studies ( $P<0.001$ ) and with 12.5 mg of naloxegol in study 04 ( $P<0.001$ ). Pain scores and daily opioid dose were similar among the three groups. Adverse events (primarily gastrointestinal) occurred most frequently in the groups treated with 25 mg of naloxegol.

**CONCLUSIONS**

Treatment with naloxegol, as compared with placebo, resulted in a significantly higher rate of treatment response, without reducing opioid-mediated analgesia. (Funded by AstraZeneca; KODIAC-04 and KODIAC-05 ClinicalTrials.gov numbers, NCT01309841 and NCT01323790, respectively.)

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OPIOIDS ARE A FAMILY OF COMPOUNDS that includes natural, synthetic, and semi-synthetic agents. Because of their centrally mediated analgesic properties, opioids play a critical role in the management of acute and chronic pain. In the United States, more than 240 million opioid prescriptions are dispensed per year, the majority for noncancer pain such as back pain and other musculoskeletal ailments.<sup>1</sup>

Among patients taking opioids, 40 to 90% have constipation and other gastrointestinal side effects,<sup>2-5</sup> which can adversely affect adherence to pain-medication regimens and quality of life.<sup>3</sup> Constipation is the most common<sup>3,4,6</sup> and most bothersome<sup>3</sup> gastrointestinal side effect reported by patients taking opioids.<sup>3,4,6</sup> Opioid-induced constipation results from the binding of opioid agonists to  $\mu$ -opioid receptors located in the enteric nervous system, which leads to increased nonpropulsive contractions and inhibition of water and electrolyte secretion.<sup>7,8</sup> Opioid-agonist binding to these receptors also triggers inhibition of gastric emptying, an increase in pyloric tone, delay of transit throughout the small and large intestines, an increase in resting anal-sphincter pressure, and a decrease in secretion of electrolytes and water into the intestinal lumen, as well as a concurrent increase in the net absorption of luminal fluid.<sup>2</sup>

Dietary modifications, lifestyle changes, and laxatives are used to treat opioid-induced constipation, but their efficacy is limited.<sup>9,10</sup> A more recent approach is the development of peripherally acting  $\mu$ -opioid receptor antagonists.<sup>11</sup> These agents limit the effects of opioids on the gastrointestinal tract while preserving centrally mediated analgesia.<sup>11</sup> Two such agents, methylnaltrexone and alvimopan, are currently available, but the use of methylnaltrexone is restricted by the need for subcutaneous administration and a narrow indication (treatment of opioid-induced constipation in patients with advanced medical illness), and alvimopan is approved only for shortening the course of postoperative ileus.<sup>12,13</sup>

Naloxegol is a pegylated derivative of the  $\mu$ -opioid receptor antagonist naloxone and is a neutral antagonist of the  $\mu$ -opioid receptor *in vitro*.<sup>14,15</sup> Pegylation confers P-glycoprotein transporter-substrate properties<sup>16</sup> and thus limits the ability of naloxegol to cross the blood-brain barrier.<sup>14</sup> In a phase 2b trial, naloxegol at a daily dose of 25 or 50 mg increased the frequency of sponta-

neous bowel movements in patients with opioid-induced constipation, whereas 5 mg had no significant effect.<sup>17</sup> The 25-mg dose was selected for phase 3 development on the basis of the safety and efficacy profile in the phase 2b trial.<sup>17</sup> In the present study, we included a 12.5-mg dose to continue exploring the threshold for the minimally effective dose.

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## METHODS

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### PATIENTS AND STUDY DESIGN

We conducted two identical multicenter, randomized, double-blind, parallel-group, placebo-controlled phase 3 studies (KODIAC-04 [study 04] and KODIAC-05 [study 05]) at 115 centers (study 04) and 142 centers (study 05) in the United States and Europe. Study 04 was conducted from March 14, 2011, to August 16, 2012, and study 05 was conducted from March 28, 2011, to September 20, 2012. We enrolled outpatients 18 to 84 years of age who had been taking an oral opioid for noncancer pain, at a stable total daily dose of 30 to 1000 mg of morphine (or the equivalent), for 4 weeks or longer.

Eligible patients reported symptoms of active opioid-induced constipation (<3 spontaneous bowel movements per week with one or more of the following symptoms: hard or lumpy stools, straining, or a sensation of incomplete evacuation or anorectal obstruction in at least 25% of bowel movements during the 4 weeks before screening). For patients whose symptoms met these criteria, opioid-induced constipation was confirmed over a 2-week period on the basis of data from daily electronic diaries. In the diaries, patients recorded information on bowel-movement occurrence, stool consistency, severity of straining, completeness of evacuation, pain level, rescue laxative use, and opioid-medication use for breakthrough pain. Patients who subsequently underwent randomization continued to record their symptoms in electronic diaries throughout the treatment period.

Exclusion criteria were uncontrolled pain despite opioid analgesic therapy (patients in the study were required to be receiving a stable maintenance regimen for pain with no anticipated change for the duration of the study), cancer within 5 years before enrollment, conditions or use of medications associated with diarrhea or constipation (other than opioid-induced

constipation), evidence of gastrointestinal obstruction, and conditions that confer an increased risk of bowel perforation.

Eligible patients who had confirmed opioid-induced constipation and who continued to meet study criteria were stratified on the basis of prescreening laxative-response status and randomly assigned in a 1:1:1 ratio to receive 25 mg of naloxegol (25-mg group), 12.5 mg of naloxegol (12.5-mg group), or placebo (placebo group) once daily for 12 weeks. The enrollment procedure ensured that 50% or more of patients randomly assigned to a group were patients with an inadequate response to laxatives, defined as those who took medication from one or more laxative classes for a minimum of 4 days within 2 weeks before screening and whose symptoms were rated as moderate, severe, or very severe in at least one of the four stool-symptom domains on the baseline laxative-response questionnaire.

Throughout confirmation and treatment, laxatives and other bowel-treatment regimens (e.g., prune juice or herbal products) were not allowed; however, if a bowel movement had not occurred within 72 hours after the last recorded bowel movement, the use of bisacodyl as a rescue medication was permitted. Only bisacodyl (10 to 15 mg; maximum of 3 doses per episode) followed by one-time use of an enema (if necessary) was allowed as rescue treatment. Opioid antagonists, mixed antagonists, and strong inhibitors of cytochrome P-450 3A4 and P-glycoprotein were prohibited.

The studies were conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonisation. An ethics committee or institutional review board at each study site approved the final study protocol and informed-consent form. All patients provided written informed consent at screening, before any study procedures were performed.

The study protocols, available with the full text of this article at NEJM.org, were designed by AstraZeneca with input from the academic authors, who served as consultants to the sponsor. Study conduct, monitoring, and data analysis were performed by Quintiles, a contract research organization, 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 and statistical analysis. The first author wrote the first draft of the Introduction and

Discussion without any writing assistance, revised the first draft of the Methods and Results (as prepared by a medical writer contracted by the sponsor), and reviewed and revised all subsequent versions of the manuscript. Editorial support was provided by Complete Healthcare Communications and was paid for by the sponsor. The decision to submit the manuscript for publication was made collectively by the academic authors and the study sponsor.

#### ASSESSMENTS

The primary end point was the response rate during the 12-week treatment period. Response was defined as three or more spontaneous bowel movements (bowel movements without the use of rescue laxative treatment in the previous 24 hours) per week and an increase of one or more spontaneous bowel movements over baseline for at least 9 of 12 treatment weeks and at least 3 of the final 4 treatment weeks. If patients did not record electronic diary entries for at least 4 of 7 days in a given week, they were classified as not having a treatment response during those weeks. Patients who discontinued the study prematurely were classified as not having a response during the weeks after discontinuation.

The key secondary efficacy end points were the response rate in the subpopulation of patients with an inadequate response to laxatives before study enrollment, the time to the first postdose spontaneous bowel movement, and the mean number of days per week with one or more spontaneous bowel movements. Additional secondary efficacy end points were the mean number of spontaneous bowel movements per week, severity of straining (measured on a 5-point scale, with 1 denoting no straining and 5 denoting an extreme amount of straining), stool consistency (assessed on the Bristol stool scale), and rescue laxative use.

Safety-related variables included adverse events and changes in mean daily opioid dose (morphine-equivalent dose in milligrams per day) and pain score (on a numeric rating scale, with 0 denoting no pain, and 10 denoting the worst imaginable pain).<sup>18</sup> Opioid-withdrawal signs were assessed with the use of the modified Himmelsbach scale.<sup>19,20</sup> Major cardiovascular adverse events and serious gastrointestinal adverse events related to bowel perforation were evaluated by independent external adjudication

committees whose members were unaware of the study-group assignments. Changes in vital signs and electrocardiographic characteristics were also monitored on the basis of observations from a preclinical telemetry study in dogs, which showed small, transient decreases in blood pressure and increases in heart rate at maximum mean plasma concentrations of naloxegol that were five times as high as the mean concentrations associated with the therapeutic dose of 25 mg used in the present study.

#### STATISTICAL ANALYSIS

On the basis of data from the 4-week phase 2b trial, in which the response rates were 60% and 35% with active treatment and placebo, respectively,<sup>17</sup> we calculated that a sample of 105 patients in each study group would provide 90% power at a two-sided alpha level of 2.5%. We assumed that the magnitude of effect observed over a 12-week period would be similar to that observed over the 4-week period in the earlier study, and our protocol ensured that patients with an inadequate response to laxatives before enrollment would make up 50% of the total sample; hence, we planned to randomly assign 210 patients to each study group.

Efficacy analyses were performed in the intention-to-treat population; unadjusted P values are presented throughout. A Bonferroni-Holm procedure, with fixed-sequence testing of the primary and key secondary end points within groups, was used to control for multiple comparisons. As a result, in the sequential testing, a P value of less than 0.025 was considered to indicate statistical significance of the treatment response in the 25-mg group and a P value of less than 0.05 was considered to indicate significance for the 12.5-mg group, as compared with the placebo group.

Key secondary variables were tested in the following order: response rate in the subpopulation of patients with an inadequate response to laxatives before enrollment (analyzed with the use of a chi-square test), time to first postdose spontaneous bowel movement (analyzed by means of the log-rank test, stratified according to the response to laxatives before enrollment), and number of days per week with one or more spontaneous bowel movements (analyzed with the use of a mixed-model repeated-measures approach). Mixed-model repeated-measures models included adjustment for fixed effects of treat-

ment, baseline value of the dependent variable, week, treatment-by-week interaction, and prescreening laxative-response status, with center and patient as random effects. Safety analyses were conducted for patients in the intention-to-treat population who had received one or more doses of the study drug.

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## RESULTS

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#### PATIENTS

Baseline characteristics were balanced across the study groups and were similar between the two studies (Table 1, and Table S1 in the Supplementary Appendix, available at NEJM.org). The most common reason for opioid use was back pain (in 56.0% and 56.8% of the participants in studies 04 and 05, respectively). Other reasons were arthritis, joint pain, or fibromyalgia pain (in 18.1% and 21.6% of the participants in studies 04 and 05, respectively); headache, migraine, neuralgia, or other pain syndrome (5.9% and 4.5%); and other conditions causing pain (primarily musculoskeletal disorders) (19.7% and 17.1%). The mean duration of opioid use at baseline was 3.6 years in study 04 and 3.7 years in study 05. The majority of patients had taken a laxative in the 2 weeks before enrollment (71% in both studies); most of these patients had used laxatives from one drug class (68.3% and 66.9% in studies 04 and 05, respectively) or two drug classes (25.8% and 26.9%), most commonly stimulants (61.9% and 52.9%) and stool softeners (28.9% and 31.9%). More than 50% of patients in studies 04 and 05 (54.6% and 53.2%, respectively) were classified as having an inadequate laxative response. The details of the enrollment and exclusion of patients and the assignment of patients to study groups for both studies are shown in Figures S1A and S1B in the Supplementary Appendix.

#### EFFICACY

In study 04, a significantly higher response rate (the primary end point) was achieved with both doses of naloxegol than with placebo (12.5 mg,  $P=0.02$ ; 25 mg,  $P=0.001$ ) (Fig. 1A). In study 05, a significantly higher response rate was seen with the 25-mg dose ( $P=0.02$ ) but not with the 12.5-mg dose ( $P=0.20$ ). In study 04, the response rate was increased by 11.4 percentage points (95% confidence interval [CI], 2.4 to 20.4) with the 12.5-mg dose and by 15.0 percentage points (95% CI, 5.9 to 24.0) with the 25-mg dose, as

**Table 1. Demographic and Baseline Clinical Characteristics of the Intention-to-Treat Population.\***

Characteristic	Study 04			Study 05		
	Placebo (N=214)	Naloxegol, 12.5 mg (N=213)	Naloxegol, 25 mg (N=214)	Placebo (N=232)	Naloxegol, 12.5 mg (N=232)	Naloxegol, 25 mg (N=232)
Age — yr	52.9±10.0	51.9±10.4	52.2±10.3	52.3±11.6	52.0±11.0	51.9±12.1
Female sex — no. (%)	140 (65.4)	135 (63.4)	118 (55.1)	145 (62.5)	149 (64.2)	147 (63.4)
Race — no. (%)†						
White	160 (74.8)	164 (77.0)	173 (80.8)	183 (78.9)	187 (80.6)	189 (81.5)
Black	44 (20.6)	42 (19.7)	38 (17.8)	44 (19.0)	41 (17.7)	40 (17.2)
Asian	4 (1.9)	5 (2.3)	1 (0.5)	0	1 (0.4)	0
Other	6 (2.8)	2 (0.9)	2 (0.9)	5 (2.2)	3 (1.3)	3 (1.3)
Duration of current opioid use — mo	39.5±39.4	44.4±47.3	44.5±47.8	43.0±51.4	48.5±48.7	40.9±41.6
Opioid dose — mg/day‡	135.6±145.8	139.7±167.4	143.2±150.1	119.9±103.8	151.7±153.0	136.4±134.3
Characteristics of opioid-induced constipation						
Spontaneous bowel movements per week — no.	1.4±0.89	1.4±0.85	1.3±1.11	1.5±0.95	1.6±1.05	1.3±0.85
Score for severity of straining§	3.3±0.78	3.1±0.79	3.2±0.84	3.3±0.81	3.1±0.82	3.2±0.82
Score for stool consistency¶	2.8±1.22	2.9±1.20	2.9±1.16	3.0±1.29	3.0±1.32	2.8±1.26
Laxative use — no. (%)						
Within previous 6 mo	177 (82.7)	184 (86.4)	181 (84.6)	197 (84.9)	189 (81.5)	194 (83.6)
Within previous 2 wk	151 (70.6)	140 (65.7)	166 (77.6)	173 (74.6)	156 (67.2)	166 (71.6)
Inadequate response to laxatives — no. (%)	118 (55.1)	115 (54.0)	117 (54.7)	121 (52.2)	125 (53.9)	124 (53.4)

\* Plus–minus values are means ±SD. Numbers of patients differed between the intention-to-treat population (641 in study 04 and 696 in study 05) and the population of patients randomly assigned to a study group (652 in study 04 and 700 in study 05) because 11 patients in study 04 and 4 patients in study 05 were found to be participating at more than one center within the program and were excluded from the intention-to-treat population. No notable between-group differences in demographic or clinical characteristics were observed; a formal statistical comparison was not performed.

† Race was self-reported.

‡ This characteristic was assessed among patients in the safety-analysis set, which included all patients in the intention-to-treat population who received at least one dose of drug.

§ Severity of straining was measured on the following scale: 1, not at all; 2, a little bit; 3, a moderate amount; 4, a great deal; and 5, an extreme amount.

¶ Stool consistency was assessed on the Bristol stool scale (types 1 through 7, with 1 denoting small, hard, lumpy stool and 7 denoting watery stool).

|| Patients with an inadequate response to laxatives were those who took laxatives in one or more laxative classes for a minimum of 4 days within 2 weeks before screening and had ratings of moderate, severe, or very severe on one or more of the four stool-symptom domains in the baseline laxative-response questionnaire.

compared with placebo; in study 05, the differences in the response rate between active treatment and placebo were 5.6 percentage points (95% CI, –2.9 to 14.1) with the 12.5-mg dose and 10.3 percentage points (95% CI, 1.7 to 18.9) with the 25-mg dose. For the primary end point in both studies, there was no significant interaction between treatment and baseline daily opioid dose with either dose of naloxegol versus placebo ( $P \geq 0.11$ ).

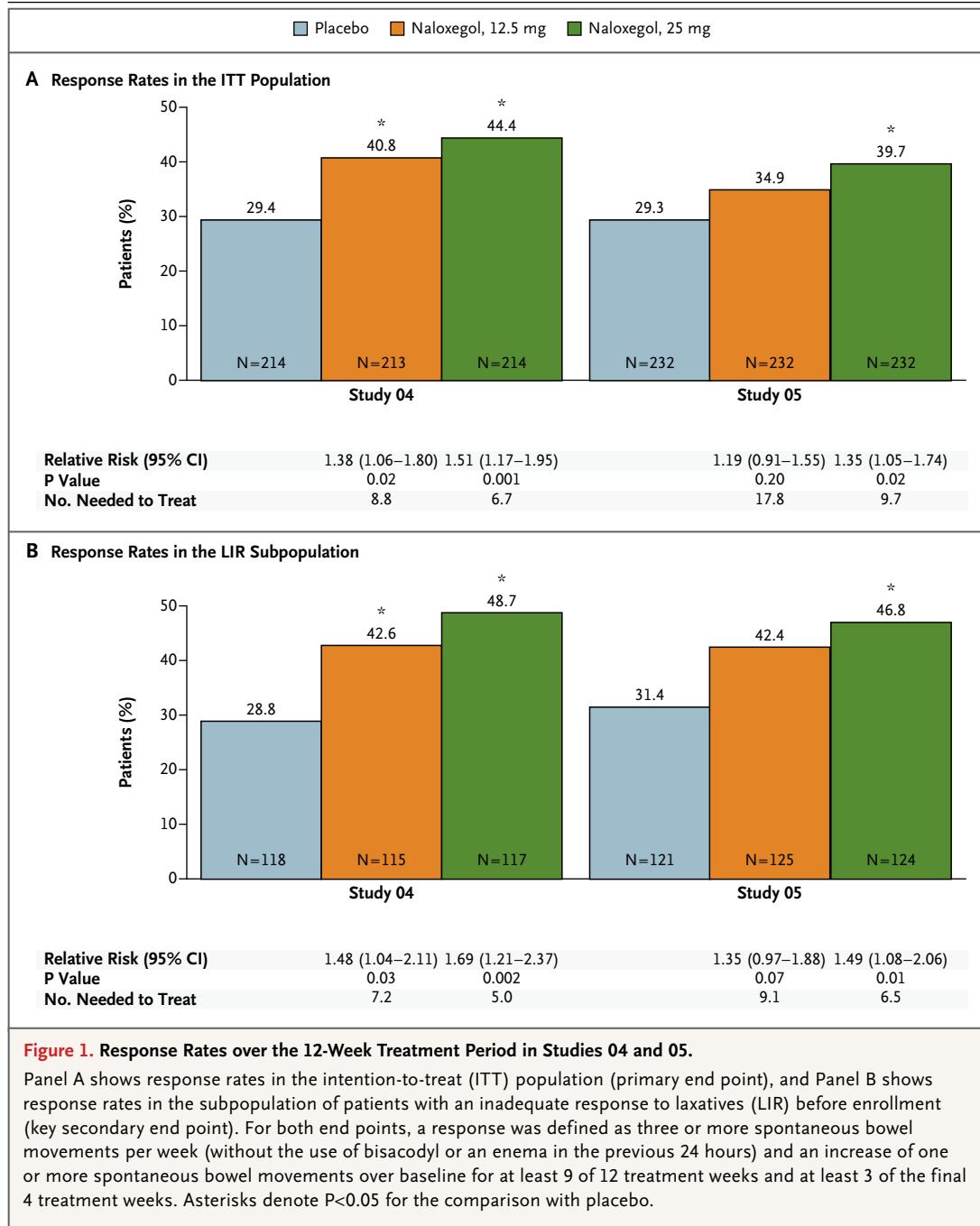
In the subpopulation of participants with an inadequate response to laxatives before study enrollment, response rates were significantly

higher in the 25-mg group than in the placebo group in both studies and were significantly higher in the 12.5-mg group in study 04 (Fig. 1B). In study 04, the response-rate differences between active treatment and placebo were 13.8 percentage points (95% CI, 1.6 to 26.0) with the 12.5-mg dose and 19.9 percentage points (95% CI, 7.7 to 32.1) with the 25-mg dose; in study 05, the differences were 11.0 percentage points (95% CI, –1.0 to 23.0) with the 12.5-mg dose and 15.4 percentage points (95% CI, 3.3 to 27.4) with the 25-mg dose. In study 05, because the primary end point did not differ significantly between

the 12.5-mg group and the placebo group, significance could not be claimed for any of the key secondary end points in the comparison of the 12.5-mg dose with placebo, according to the multiple-testing procedure. Nominal P values are provided in Figure 1 for all analyses.

The time to the first postdose spontaneous bowel movement was significantly shorter with

either naloxegol dose than with placebo in study 04 and was significantly shorter with the 25-mg dose than with placebo in study 05 (P<0.001 for all comparisons) (Fig. S2A in the Supplementary Appendix). In studies 04 and 05, the median time to the first spontaneous bowel movement was 5.9 and 12.0 hours, respectively, in the 25-mg group, as compared with 35.8 and 37.2 hours in



the placebo group. There was a significant increase in the mean number of days per week with one or more spontaneous bowel movements from week 1 to week 12 with both doses of naloxegol in study 04 and with the 25-mg dose in study 05 ( $P < 0.001$  for all comparisons); this effect remained consistent over the 12-week treatment period (Fig. S2B in the Supplementary Appendix).

The number of spontaneous bowel movements per week increased in association with naloxegol treatment over the 12-week period, with both studies showing a significantly greater effect in the naloxegol groups than in the placebo groups (Table 2). Greater improvements in straining, stool consistency, and frequency of days with complete spontaneous bowel movements were observed in the 25-mg group in both stud-

ies and in the 12.5-mg group in study 05, as compared with the placebo group (Table 2). Over the 12-week period, the proportions of patients who used bisacodyl at least once as a rescue laxative in the placebo group, 12.5-mg group, and 25-mg group were 72.0, 63.4, and 54.7%, respectively, in study 04 and 70.7, 57.3, and 57.3% in study 05.

#### SAFETY

The mean duration of exposure to the study drug was similar in all groups in both studies (range, 72.4 to 77.5 days) (Table S2 in the Supplementary Appendix). The incidence of overall adverse events and the incidence of adverse events leading to study discontinuation were higher in the 25-mg group than in the 12.5-mg group or the placebo group (Table 3). Adverse events leading to study discon-

**Table 2. Secondary Efficacy End Points.\***

Variable	Study 04			Study 05		
	Placebo (N=211)	Naloxegol, 12.5 mg (N=211)	Naloxegol, 25 mg (N=212)	Placebo (N=231)	Naloxegol, 12.5 mg (N=228)	Naloxegol, 25 mg (N=226)
No. of spontaneous bowel movements per week						
Change from baseline†	2.02±0.18	2.56±0.18	3.02±0.18	2.10±0.18	2.62±0.18	3.14±0.19
Difference from placebo (95% CI)		0.54 (0.12 to 0.96)‡	0.99 (0.57 to 1.41)§		0.52 (0.06 to 0.98)‡	1.04 (0.58 to 1.51)§
Severity of straining per week						
Change from baseline†¶	-0.54±0.05	-0.64±0.05	-0.73±0.05	-0.48±0.06	-0.67±0.06	-0.80±0.06
Difference from placebo (95% CI)		-0.09 (-0.23 to 0.04)	-0.18 (-0.32 to -0.05)¶		-0.19 (-0.32 to -0.06)¶	-0.32 (-0.45 to -0.18)§
Stool consistency per week						
Change from baseline†**	0.47±0.07	0.53±0.07	0.66±0.07	0.26±0.06	0.54±0.07	0.71±0.07
Difference from placebo (95% CI)		0.05 (-0.12 to 0.23)	0.18 (0.01 to 0.36)‡		0.28 (0.12 to 0.45)¶	0.45 (0.29 to 0.62)§
Percentage of days per week with a complete spontaneous bowel movement						
Change from baseline†	18.45±1.72	22.31±1.73	27.04±1.75	16.76±1.86	23.48±1.88	27.20±1.93
Difference from placebo (95% CI)		3.87 (-0.66 to 8.39)	8.59 (4.04 to 13.14)§		6.72 (2.37 to 11.06)¶	10.43 (6.03 to 14.84)§

\* Plus-minus values are means ±SE. The secondary efficacy end points were not included in the multiple testing procedure. Nominal P values have not been adjusted for multiple comparisons.

† Values are from the repeated-measures analysis; the least-squares mean is presented.

‡  $P < 0.05$  for the comparison with placebo.

§  $P < 0.001$  for the comparison with placebo.

¶ Severity of straining was measured on the following scale: 1, not at all; 2, a little bit; 3, a moderate amount; 4, a great deal; 5, an extreme amount.

||  $P < 0.01$  for the comparison with placebo.

\*\* Stool consistency was assessed on the Bristol stool scale (types 1 through 7).

tinuation occurred more commonly in the 25-mg groups and were primarily driven by differences in gastrointestinal adverse events. The adverse events leading to discontinuation in at least three patients in the 25-mg group were diarrhea (2.8% of patients), abdominal pain (1.9%), and upper abdominal pain (1.4%) in study 04 and abdominal pain (3.9%), diarrhea (3.4%), nausea (1.7%), and vomiting (1.7%) in study 05. Individual serious adverse events were infrequent and similar in type and frequency across the three groups in both studies; no individual event was reported in more than two patients in any group in either study (Table S3 in the Supplementary Appendix).

There were two deaths in study 04, both in the 12.5-mg group (one from advanced-stage non-small-cell lung cancer diagnosed during the study, and the other from complications of heart-valve replacement). Adjudicated major cardiovascular events were reported in two patients in study 04 and two patients in study 05 (Table 3). Only one major cardiovascular event was considered by the investigator to be related to the study drug, and it occurred in the placebo group. No serious gastrointestinal events were adjudicated as probable bowel perforation. No notable between-group differences in mean changes from baseline in vital signs or electrocardiographic characteristics were observed.

The mean daily opioid doses remained stable during the studies; the mean changes from baseline to week 12 in the placebo group, 12.5-mg group, and 25-mg group were -1.8, -2.3, and 0.4 mg per day, respectively, in study 04 and -0.3, -1.3, and 0.1 mg per day in study 05. The mean changes from baseline in the pain score during the 12-week treatment period were small and not clinically significant (changes in the placebo group, 12.5-mg group, and 25-mg group: -0.2, -0.3, and -0.2 points, respectively, in study 04 and -0.1, -0.1, and 0 points in study 05).

Adverse events reported by the investigator as the drug-withdrawal syndrome were infrequent (Table 3). Most patients had no change from their baseline score on the modified Himmelsbach opioid-withdrawal scale at any study visit; in the placebo group, 12.5-mg group, and 25-mg group, the scores showed no increase from baseline in 77.9, 84.8, and 79.3% of patients, respectively, in study 04 and in 80.1, 71.6, and 75.0% of patients in study 05. Score changes of 3 points or more were infrequent in all study groups (3.8,

1.4, and 3.3% of patients, respectively, in study 04 and 2.2, 2.6, and 3.9% in study 05).

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## DISCUSSION

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The results of these two large phase 3 trials confirm the efficacy of the orally administered peripheral  $\mu$ -opioid receptor antagonist naloxegol for the treatment of opioid-induced constipation in patients with noncancer pain. In both studies, naloxegol at a dose of 25 mg was associated with an increased rate of response (10 to 15 percentage points higher than the response with placebo) over a period of 12 weeks. In study 04, naloxegol at a dose of 12.5 mg was also associated with a significantly higher response rate than placebo. In addition, other constipation-related end points, including the time to the first spontaneous bowel movement, mean number of days per week with one or more spontaneous bowel movements, number of weekly spontaneous bowel movements, severity of straining, and stool consistency, were improved in the patients who received naloxegol, as compared with those who received placebo.

In a prespecified analysis, the clinical benefits of naloxegol in patients with opioid-induced constipation and an inadequate response to laxatives were consistent with the benefits in the overall study population. In clinical practice, osmotic and stimulant laxatives are likely to be used before more expensive prescription medications. Thus, the finding that naloxegol proved beneficial in patients who had persistent symptoms of opioid-induced constipation despite using standard laxative therapies is of potential importance.

The most commonly reported adverse effects with naloxegol were gastrointestinal (abdominal pain, diarrhea, nausea, and vomiting) and appeared to be dose-ordered in frequency, occurring more commonly in the 25-mg group. Most adverse events were mild to moderate in severity and occurred shortly after initiation of naloxegol treatment. Adverse events leading to study discontinuation were most common with the 25-mg dose of naloxegol. Severe adverse events were uncommon and evenly distributed among the study groups. Major cardiovascular events were rare, and their occurrence was balanced across the groups in both studies. This is reassuring, given the concern about cardiovascular safety with alvimopan, another peripherally acting

**Table 3. Adverse Events.**

Adverse Event	Study 04			Study 05		
	Placebo (N=213)	Naloxegol, 12.5 mg (N=211)	Naloxegol, 25 mg (N=214)	Placebo (N=231)	Naloxegol, 12.5 mg (N=230)	Naloxegol, 25 mg (N=232)
	<i>number of patients (percent)</i>					
Any adverse event*	100 (46.9)	104 (49.3)	131 (61.2)	136 (58.9)	137 (59.6)	160 (69.0)
Adverse events leading to discontinuation	12 (5.6)	9 (4.3)	22 (10.3)	12 (5.2)	12 (5.2)	24 (10.3)
Serious adverse events†	11 (5.2)	11 (5.2)	7 (3.3)	12 (5.2)	14 (6.1)	8 (3.4)
Deaths	0	2 (0.9)	0	0	0	0
Adverse events reported in >5% of patients in any group in either study‡						
Abdominal pain	7 (3.3)	18 (8.5)	27 (12.6)	18 (7.8)	25 (10.9)	44 (19.0)
Diarrhea	9 (4.2)	7 (3.3)	20 (9.3)	10 (4.3)	18 (7.8)	21 (9.1)
Nausea	10 (4.7)	15 (7.1)	16 (7.5)	10 (4.3)	14 (6.1)	20 (8.6)
Flatulence	4 (1.9)	9 (4.3)	12 (5.6)	7 (3.0)	4 (1.7)	14 (6.0)
Upper abdominal pain	4 (1.9)	3 (1.4)	11 (5.1)	3 (1.3)	5 (2.2)	6 (2.6)
Vomiting	7 (3.3)	3 (1.4)	6 (2.8)	6 (2.6)	7 (3.0)	14 (6.0)
Headache	4 (1.9)	5 (2.4)	8 (3.7)	8 (3.5)	12 (5.2)	12 (5.2)
Back pain	5 (2.3)	0	7 (3.3)	4 (1.7)	12 (5.2)	12 (5.2)
Adverse events of special interest*						
Adjudicated as major cardiovascular events§	0	1 (0.5)¶	1 (0.5)¶	2 (0.9)¶	0	0
Identified as drug-withdrawal syndrome	1 (0.5)	1 (0.5)	1 (0.5)	0	1 (0.4)**	4 (1.7)

\* Events that occurred during the treatment period or the follow-up period are included.

† A serious adverse event was defined as an adverse event occurring during any study phase and fulfilling one or more of the following criteria: resulted in death; was immediately life-threatening; required inpatient hospitalization or prolongation of existing hospitalization; resulted in persistent or clinically significant disability, incapacity, or substantial disruption of the ability to conduct normal life functions; was a congenital abnormality or birth defect; or was an important medical event that might have jeopardized the patient or required medical intervention to prevent one of the above outcomes.

‡ Events that occurred during the treatment period only are included.

§ Events adjudicated by an independent, blinded adjudication committee as death from cardiovascular causes, myocardial infarction, or stroke are included.

¶ The patient had an acute myocardial infarction.

|| The patient died from cardiovascular causes.

\*\* The patient ran out of opioid medication.

$\mu$ -opioid antagonist.<sup>13</sup> A peripheral site of action for naloxegol was supported by the absence of significant changes in opioid doses and pain scores during the study, which indicated the preservation of centrally mediated analgesia.

Improvements from baseline in spontaneous bowel movements were similar in magnitude in the two studies. It is unclear why differences in response rates associated with naloxegol versus placebo were numerically lower in study 05 than in study 04 or why the 12.5-mg dose was associ-

ated with a significantly higher response rate than placebo only in study 04. Differences in response rates are probably not due to clinical characteristics of the specific study populations, because naloxegol was associated with numerically higher response rates than was placebo, when pooled data were analyzed across predefined subgroups (including groups based on age, race, sex, body-mass index, and opioid dose). However, the 25-mg dose of naloxegol led to significant differences in response rates and dose-

ordered improvements in constipation status as reflected by the secondary end points, indicating a robust pharmacodynamic effect in both studies.

In summary, our two studies showed that treatment with the pegylated  $\mu$ -opioid receptor antagonist naloxegol, a member of an emerging class of drugs that decrease gastrointestinal side effects of opioids without reducing centrally mediated analgesia, achieved response rates that

were increased by 10 to 15 percentage points, as compared with placebo, in patients with chronic noncancer pain and opioid-induced constipation.

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