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A Randomized, Multicenter, Prospective, Crossover, Open-Label Study of Factors Associated With Patient Preferences for Naloxegol or PEG 3350 for Opioid-Induced Constipation

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OBJECTIVES: **To determine patient preference for treating opioid-induced constipation (OIC) using naloxegol or polyethylene glycol (PEG) 3350 in patients receiving opioids for noncancer pain.**

METHODS: **This crossover study included two 2-week active treatment periods, each preceded by a 1-week washout period (NCT03060512). Individuals with baseline Bowel Function Index scores ≥30 were randomized to 1 of 2 treatment sequences (naloxegol/PEG 3350 or PEG 3350/naloxegol). Patient preference (primary end point) was measured at the end of the second treatment period.**

RESULTS: **Of 276 patients randomized, 246 completed both treatment periods and reported preference (per protocol). Similar proportions of patients reported overall preference for naloxegol (50.4%) or PEG 3350 (48.0%; $P = 0.92$); 1.6% reported no preference. Medication characteristics influencing preference were similar for both treatments, except convenience and working quickly, which were strong influences of preference for higher proportions of patients preferring naloxegol (69.9% and 39.0%, respectively) vs those preferring PEG 3350 (29.9% and 27.4%, respectively). Patients aged <50 years or receiving laxatives within the previous 2 weeks generally preferred naloxegol. Changes from baseline in overall Bowel Function Index and Patient Global Impression of Change scores were similar between treatments, but analyses according to treatment preference revealed clinical improvement aligned with reported preference. Safety profiles were generally consistent with known medication profiles.**

CONCLUSIONS: **Almost equal proportions of patients with OIC reported similar preference for daily naloxegol or PEG 3350 treatment, and their preference was generally supported by clinically relevant and measurable improvements in OIC symptoms.**

SUPPLEMENTARY MATERIAL accompanies this paper at http://links.lww.com/AJG/A169

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INTRODUCTION

Opioid-induced constipation (OIC) is the most common and burdensome gastrointestinal side effect of opioid therapy for the management of chronic pain (1). OIC affects approximately 41%–81% of patients receiving opioids for chronic noncancer pain (2) and is associated with a significant negative impact on health-related quality of life (3–5).

Consensus guidelines for OIC recommend over-the-counter (OTC) laxatives as first-line agents (3). Polyethylene glycol (PEG) 3350, an osmotic laxative, is one of the most commonly used OTC laxatives for patients experiencing occasional constipation, including OIC (5). Conventional laxative treatments are well tolerated and readily available but may be ineffective for treating OIC (5). In fact, OIC-related symptoms and negative effects on health-related quality of life and function often persist even in patients using laxatives. For example, in 1 study of patients experiencing moderate OIC symptoms and their impact on quality of life, only 48% were considered to be using sufficient doses of laxatives, defined as taking at least 1 laxative 4 times or more over a 2-week period (6). In a separate survey of patients with OIC, more than 50% of patients taking at least 1 laxative were experiencing moderate to very severe symptoms of abdominal pain and/or bloating (7).

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This may be due to the fact that conventional laxatives do not target the underlying pathophysiology of OIC (i.e., the activation of mu-opioid receptors in the gastrointestinal tract) (8).

Consensus recommendations also suggest that prescription treatments for OIC be considered for patients with a Bowel Function Index (BFI) score of 30 or greater and an inadequate response to OTC laxatives (3). Naloxegol, a peripherally acting mu-opioid receptor antagonist designed to specifically target the mechanism underlying OIC, has been approved by the US Food and Drug Administration for the treatment of OIC in adult patients with chronic noncancer pain, including chronic pain related to previous cancer or its treatment. Unlike OTC laxatives, naloxegol directly targets the opioid-related mechanism for inducing constipation (9).

Despite an abundance of different treatment options for OIC, there is a general lack of data on patient-reported outcomes associated with the use of these treatments. In particular, there is a paucity of direct comparative studies for prescription treatments compared with OTC laxatives. Therefore, the purposes of this study (ClinicalTrials.gov identifier: NCT03060512) were to (i) evaluate preferences for naloxegol or PEG 3350 among patients with OIC associated with chronic noncancer pain syndromes, (ii) determine factors associated with these preferences, and (iii) assess the impact of each treatment on patient-reported outcomes as measures of the clinical effectiveness of each treatment for OIC symptoms.

METHODS

Study design

This 6-week, randomized, multicenter, prospective, crossover, open-label, phase 4 study comprised 2 treatment sequence arms; each treatment sequence consisted of 2-week daily treatment periods, separated by a 1-week washout period (Figure 1). Eligible patients were randomly assigned 1:1 to 2 treatment sequences: naloxegol (Movantik; AstraZeneca Pharmaceuticals LP, Wilmington, DE; one 25-mg tablet once daily) during the first treatment period, followed by PEG 3350 (the active ingredient in MiraLAX; Bayer Corporation, Whippany, NJ; 17 g dissolved in 4–8 oz liquid once daily) during the second treatment period; or alternatively to PEG 3350 during the first treatment period, followed by naloxegol during the second treatment period (Figure 1). The ends of the first and second treatment period corresponded to visits 3 and 5, respectively. At completion of the second treatment period, patients rated their preference for 1 of the 2 treatments and the factors that contributed to their preference. This study was performed in accordance with the ethical principles of the Declaration of Helsinki and is consistent with International Conference on Harmonisation/Good Clinical Practice and applicable regulatory requirements. The clinical study protocol and amendment were approved by Independent Ethics Committees. Additional details of the study design are summarized in the Supplementary Methods (see Supplementary Digital Content 1, http://links.lww.com/AJG/A169).

Patient population

Adults aged 18–84 years meeting the Rome IV criteria for OIC and receiving a stable dose of opioids for noncancer pain were eligible for inclusion. Eligible patients had to be taking at least 30 oral morphine equivalent units (MEU) per day for at least 1 month, while maintaining stable dosing for at least 2 weeks before screening. Eligible patients were required to report at least 2 of the following new/worsening symptoms when initiating or modifying opioid dosages: fewer than 3 spontaneous bowel movements (SBMs) per week, straining (>25% of defecations), sensation of incomplete evacuation (>25% of defecations), lumpy or hard stools (>25% of defecations) (10), and/or sensation of anorectal obstruction/blockage (>25% of defecations). Patients were also required to have a BFI score of 30 or greater before the first treatment period (visits 1 and 2) and be willing to stop all laxatives and alternative bowel regimens, with the exception of the study and rescue medications for the duration of the trial. Exclusion criteria are summarized in the Supplementary Methods (see Supplementary Digital Content 1, http://links.lww.com/AJG/A169).

Study assessments

Patient-reported preference. The primary end point—patient-reported preference for naloxegol or PEG 3350—was assessed at the end of the second treatment period using a graded, 7-point, symmetrical scale (strong, moderate, or slight preference for naloxegol; no preference; slight, moderate, or strong preference for PEG 3350). Similar measures have been used in previous OIC studies and for other symptomatic conditions (e.g., migraine headaches) (11,12). For analysis purposes, responses were collapsed into 3 preference categories: prefer naloxegol, no preference, and prefer PEG 3350. Reason for preference (among

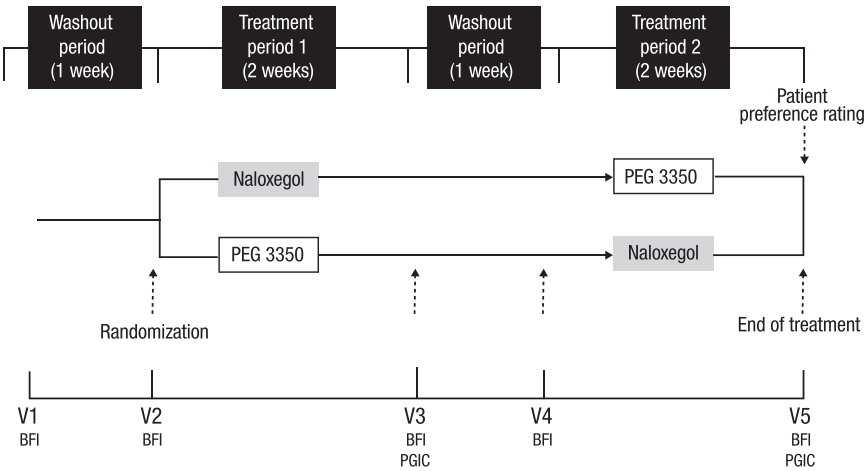

Figure 1. Study design. BFI, Bowel Function Index; PEG, polyethylene glycol; PGIC, Patient Global Impression of Change; V, visit.

patients indicating a preference) was evaluated as a secondary end point by assessing the patient-reported influence of 5 medication characteristics (efficacy, tolerability, convenience, works quickly, and works predictably) using a 4-point rating scale (0 = no influence; 1 = mildly influenced; 2 = moderately influenced; and 3 = strongly influenced).

OIC symptoms. The impact of naloxegol and PEG 3350 on OIC symptoms was also evaluated as a secondary end point using the change in the BFI score from the beginning to the end of each treatment period and the Patient Global Impression of Change (PGIC; 7-point scale: 1 = no change; 2 = almost the same; 3 = a little better; 4 = somewhat better; 5 = moderately better; 6 = better and a definite improvement; and 7 = a great deal better) score measured at the end of treatment period 1 and the end of treatment period 2 (visits 3 and 5, respectively). *Post hoc* analyses of changes in BFI scores from baseline to the end of the treatment periods (visits 3 and 5) and PGIC scores at the end of the treatment periods (visits 3 and 5) were performed to evaluate these outcomes by treatment preference.

The following exploratory end points were also evaluated in this study: stool consistency for each bowel movement (BM) using the Bristol Stool Form Scale (BSFS); straining, using a 5-point scale for each BM; BM and SBM frequency; and rescue medication usage. BM frequency, stool consistency (by BSFS), and straining were captured by patients in a daily diary.

Prespecified subgroup analyses were performed to further characterize patient preference based on the following: any laxative exposure in the 2 weeks before screening; previous use of naloxegol and/or PEG 3350 within 1 year before screening; age group; and change in opioid medication from visit 2 (used as baseline) to visit 5 (end of the second treatment period). Adverse events (AEs) were recorded throughout the study.

Statistical analyses

Sample size calculations are included in the Supplementary Methods (see Supplementary Digital Content 1, http://links.lww.com/AJG/A169). The per-protocol analysis population (all eligible patients who received the study drug, completed the treatment sequence in the randomized order, and completed the patient preference assessment at the end of the second treatment period) was used for assessment of the primary end point and the secondary end point related to patient preference. The full-analysis population (all patients receiving the study drug and completing ≥1 scheduled visit) was used for evaluating all other secondary and exploratory end points.

The Prescott test was used to evaluate the primary end point of patient preference (prefer naloxegol, no preference, and prefer PEG 3350). For analyses of the BFI change from baseline to the end of each treatment period, descriptive statistics were used to summarize the changes from the first day of both treatment periods (visits 2 and 4; baseline) to the end of both treatment periods (visits 3 and 5). For analyses of the PGIC, descriptive statistics were used to summarize the scores at the end of both treatment periods (visits 3 and 5). For analyses of the patient-reported influence of medication characteristics on overall preference, counts and percentages of subjects reporting each influence category (4-point scale) for each characteristic were summarized by treatment preference. Evaluation of all continuous secondary and exploratory variables was performed using an analysis of covariance model, with inclusion of terms for patient, treatment sequence, treatment period, and treatment. The following separate *post hoc* analyses were performed to assess preference for naloxegol or PEG 3350: demographic and baseline characteristics by preference and preference in subgroups divided by opioid dose, duration of opioid use at baseline, opioid product use, and BFI response of at least 12 (based on a reduction from the start (visit 2/visit 4) to the end (visit 3/visit 5)), which indicates a clinically meaningful change in constipation (13).

RESULTS

Study enrollment, completion, and discontinuation

Patients were recruited at 53 sites in the United States. Of 350 patients initially enrolled in the study, 74 failed screening, all of whom failed to meet the inclusion and/or exclusion criteria and

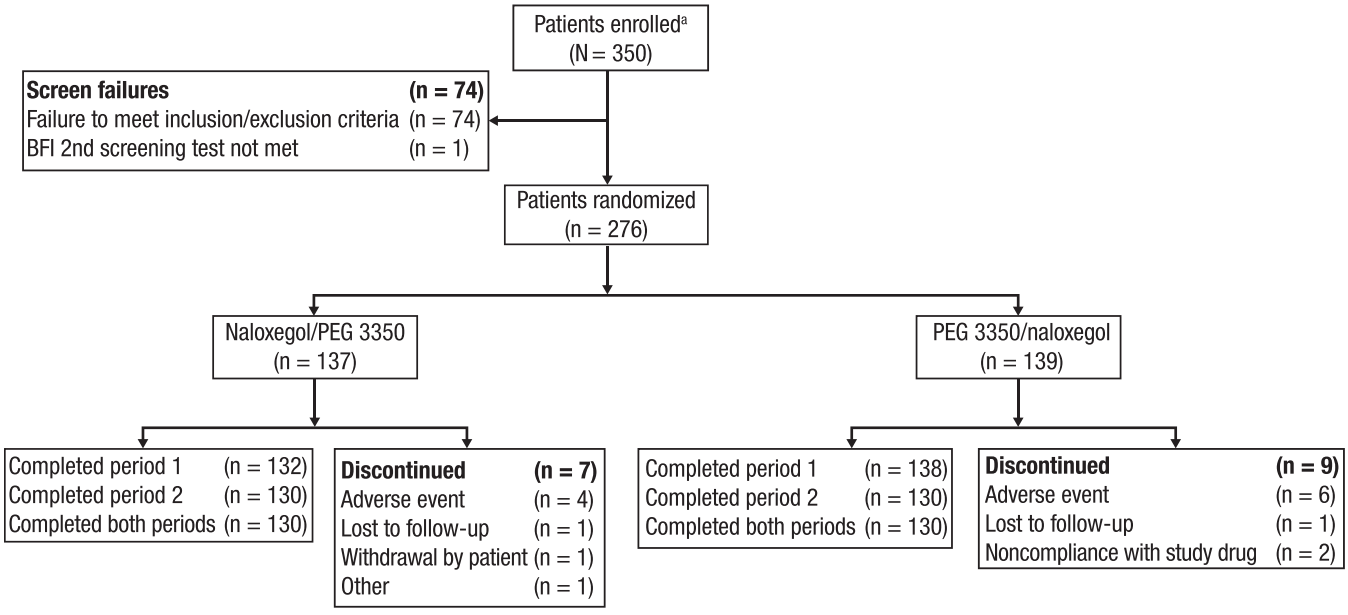

Figure 2. Patient disposition (all enrolled patients). BFI, Bowel Function Index; PEG, polyethylene glycol. [a]Total number of patients who consented.

Table 1. Demographic and baseline characteristics (full-analysis population)

Characteristic	Naloxegol/PEG 3350 (n = 132)	PEG 3350/naloxegol (n = 138)	Total (N = 270)
Age and age category, yr			
Mean (s.d.)	55.9 (9.38)	56.9 (9.65)	56.4 (9.52)
<50, n (%)	34 (25.8)	30 (21.7)	64 (23.7)
≥50 to <65, n (%)	77 (58.3)	80 (58.0)	157 (58.1)
≥65, n (%)	21 (15.9)	28 (20.3)	49 (18.1)
Sex, n (%)			
Female	87 (65.9)	89 (64.5)	176 (65.2)
Male	45 (34.1)	49 (35.5)	94 (34.8)
Race, n (%)			
White	101 (76.5)	113 (81.9)	214 (79.3)
Black or African	31 (23.5)	22 (15.9)	53 (19.6)
Asian	0 (0.0)	2 (1.4)	2 (0.7)
American Indian or Alaska Native	0 (0.0)	1 (0.7)	1 (0.4)
BMI, kg/m^2, mean (s.d.)[a]	31.0 (7.94)	31.8 (7.25)	31.5 (7.59)
Previous use of naloxegol or PEG 3350 within 1 yr of the study, n (%)			
Naloxegol only	11 (8.3)	4 (2.9)	15 (5.6)
PEG 3350 only	16 (12.1)	21 (15.2)	37 (13.7)
None	105 (79.5)	113 (81.9)	218 (80.7)
Previous use of laxatives within 2 wk of screening, n (%)			
Any (≥1 laxative)	45 (34.1)	48 (34.8)	93 (34.4)
Any (≥2 laxatives)	4 (3.0)	12 (8.7)	16 (5.9)
PEG 3350	3 (2.3)	2 (1.4)	5 (1.9)
Naloxegol	0 (0.0)	0 (0.0)	0 (0.0)
None	87 (65.9)	90 (65.2)	177 (65.6)
BFI score,[b] mean (s.d.)			
BFI score at naloxegol start[c]	71.9 (16.21)	59.0 (22.18)	65.4 (20.48)
BFI score at PEG 3350 start[d]	63.2 (23.87)	70.3 (15.58)	66.9 (20.31)
Duration of current opioid use, mo, mean (s.d.)	69.9 (65.02)	60.9 (56.72)	65.3 (60.98)
Opioid dose at screening, MEU/d, mean (s.d.)	138.2 (142.27)	121.7 (120.49)	129.7 (131.56)

BFI, Bowel Function Index; BMI, body mass index; MEU, morphine equivalent units; PEG, polyethylene glycol.
[a]Naloxegol/PEG 3350, n = 130; PEG 3350/naloxegol, n = 137; total, N = 267.
[b]Baseline BFI was measured at visits 2/4.
[c]Naloxegol/PEG 3350, n = 132; PEG 3350/naloxegol, n = 135; total, N = 267.
[d]Naloxegol/PEG 3350, n = 129; PEG 3350/naloxegol, n = 137; total, N = 266.

1 of whom also failed to meet the second BFI screening. A total of 276 were randomly assigned to 1 of the 2 treatment sequences: naloxegol/PEG 3350 (n = 137) or PEG 3350/naloxegol (n = 139) (Figure 2). A total of 270 patients (97.8%) completed the first treatment period, and 260 patients (94.2%) completed both treatment periods. The full-analysis population included 270 patients (naloxegol/PEG 3350, n = 132; PEG 3350/naloxegol, n = 138), and the per-protocol population included 246 patients (naloxegol/PEG 3350, n = 125; PEG 3350/naloxegol, n = 121). Of the 276 randomly assigned patients, 16 (5.8%) discontinued the study. Reasons for discontinuation reported for more than 1 patient included AEs (62.5% (10/16)), loss to follow-up (12.5% (2/16)), and noncompliance with study drug (12.5% (2/16)).

Demographic and baseline characteristics of study participants

Demographic and baseline characteristics were comparable for patients randomly assigned to either of the 2 treatment sequences (Table 1). Most patients in the full-analysis population were women (65%) and white (79%), with a mean age of 56 years (age range, 28–81 years). Most patients (94.1%) had musculoskeletal

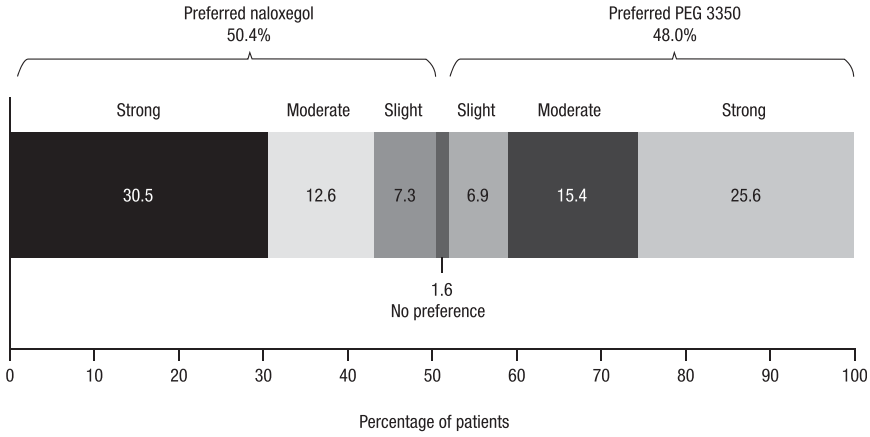

Figure 3. Patient preference ratings for naloxegol or PEG 3350 (per-protocol population). PEG, polyethylene glycol.

or connective tissue disorders. The duration of opioid therapy was 5.4 years on average and ranged from 1 month to 26.8 years. The mean opioid dose was 129.7 MEU per day at baseline, with a range of 15-1,000 MEU. Overall, the mean (s.d.) BFI score at baseline (visit after the washout period) was 65.4 (20.48) before starting naloxegol and 66.9 (20.31) before starting PEG 3350. The most commonly used opioid medications (used by ≥ 10% of patients) were oxycodone (44.8% (121/270)), hydrocodone (25.9% (70/270)), morphine sulfate (16.7% (45/270)), and tramadol (10.4% (28/270)); patients could have been using more than 1 opioid product.

Primary end point: Patient preference

In the per-protocol population, a similar proportion of patients reported a preference for naloxegol (50.4% (124/246)) and PEG 3350 (48.0% (118/246); $P = 0.92$), with most patients indicating a strong preference for 1 of the 2 treatments (Figure 3). Overall, 1.6% (4/246) of patients reported no preference. Treatment

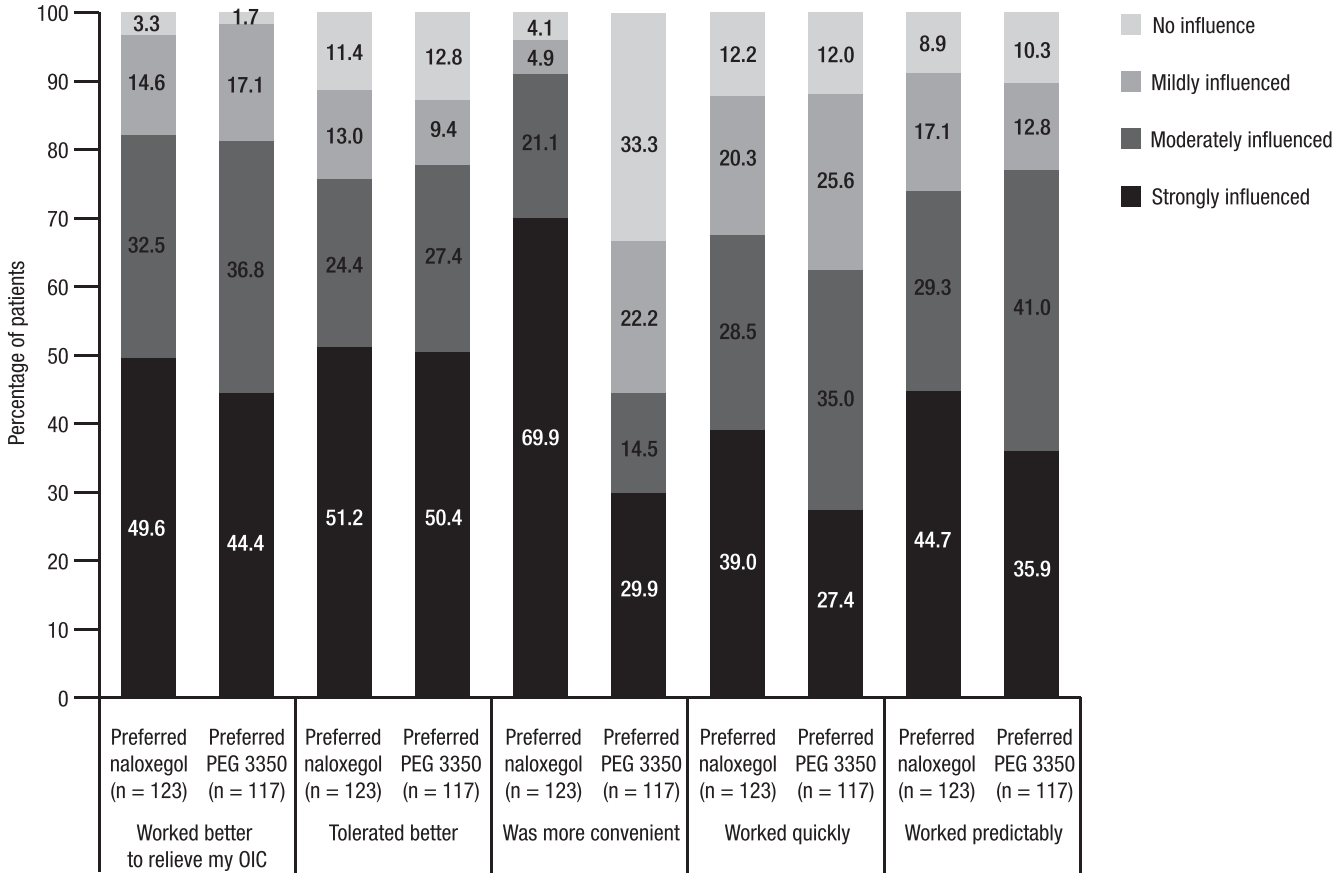

Figure 4. Patient-reported influence of medication characteristics contributing to their treatment preference. OIC, opioid-induced constipation; PEG, polyethylene glycol.

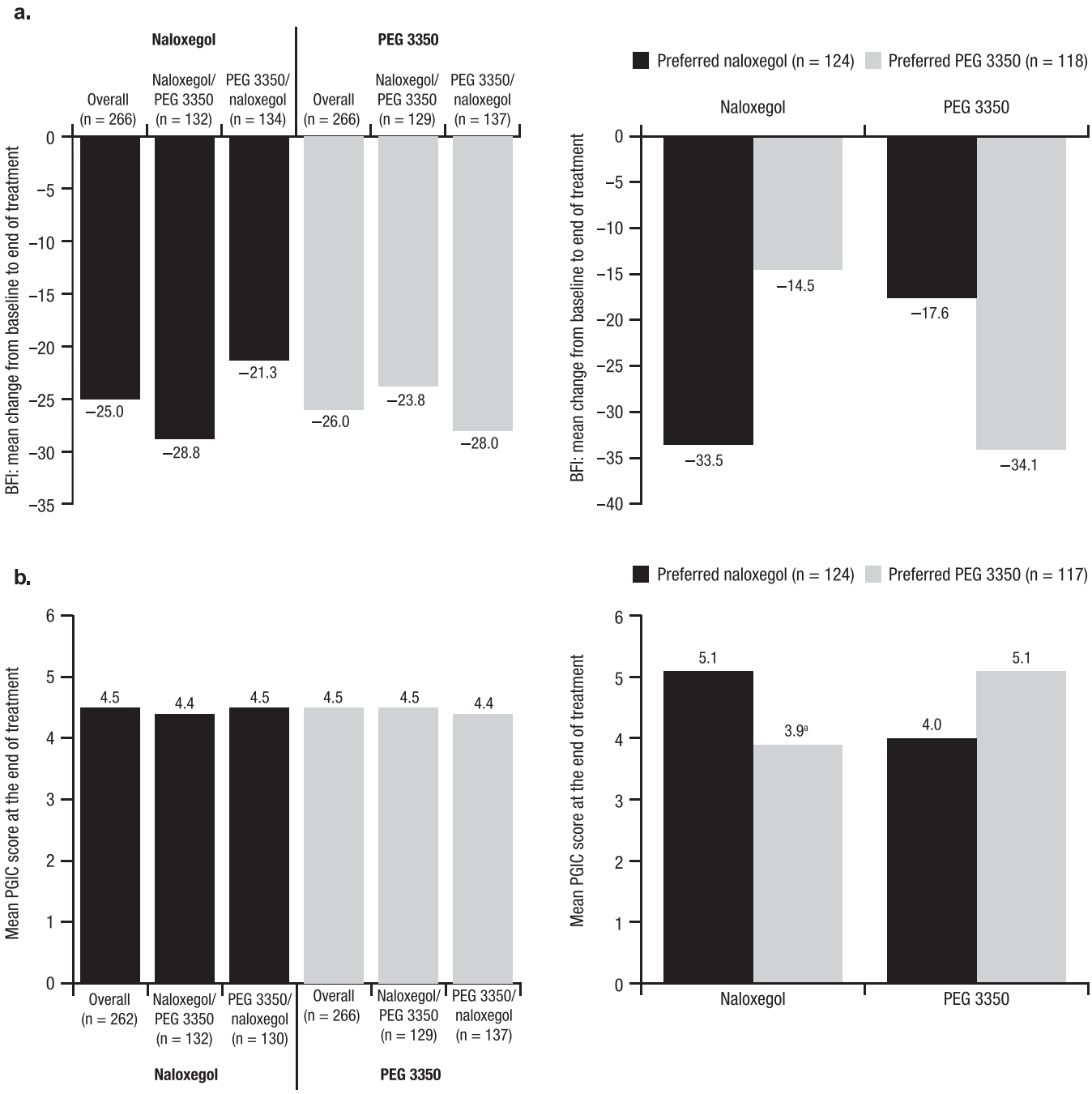

Figure 5. Clinical improvements in OIC symptoms: (**a**) change from baseline at visits 3/5 in the BFI overall (left) and by treatment preference (right); (**b**) PGIC overall (left) and by treatment preference (right). BFI, Bowel Function Index; OIC, opioid-induced constipation; PEG 3350, polyethylene glycol 3350; PGIC, Patient Global Impression of Change. [a]n = 116.

sequence did not affect preference (see Table S1, Supplementary Digital Content 1, http://links.lww.com/AJG/A169).

Secondary outcomes

Medication characteristics influencing preference. Medication characteristics influencing treatment preference were generally comparable for naloxegol and PEG 3350, with the exception of the terms "more convenient" and "worked quickly." Efficacy (i.e., "worked better to relieve my OIC") had a moderate to strong influence on patient preference for most patients, regardless of treatment preference (patients preferring naloxegol, 82.1% (101/123); patients preferring PEG 3350, 81.2% (95/117)). Tolerability (i.e., "tolerated better") also had a moderate to strong influence on patient preference for most patients preferring naloxegol (75.6% (93/123)) and for most patients preferring PEG 3350 (77.8% (91/117)). The medication being "more convenient" was reported as having a strong influence on preference for 69.9% (86/123) of patients preferring naloxegol, but only 29.9% (35/117) of patients preferring PEG 3350. The medication having "worked quickly" was reported as having a strong influence on preference for 39.0%

Table 2. Patient preference for treatment by subgroups (prespecified analyses; per-protocol population)

Subgroup, n (%)[a]	n	Preferred naloxegol	Preferred PEG 3350	No preference
Laxative use in 2 wk before screening				
Any laxative use	84	47 (56.0)	35 (41.7)	2 (2.4)
No laxative use	162	77 (47.5)	83 (51.2)	2 (1.2)
Previous naloxegol use	0	0 (0.0)	0 (0.0)	0 (0.0)
Previous PEG 3350 use	4	2 (50.0)	2 (50.0)	0 (0.0)
Previous naloxegol and/or PEG 3350 use within 1 yr before screening				
Naloxegol only	13	9 (69.2)	3 (23.1)	1 (7.7)
PEG 3350 only	35	18 (51.4)	17 (48.6)	0 (0.0)
Both	0	0 (0.0)	0 (0.0)	0 (0.0)
None	198	97 (49.0)	98 (49.5)	3 (1.5)
Age group, yr				
<50	58	31 (53.4)	24 (41.4)	3 (5.2)
≥50 to <65	146	75 (51.4)	71 (48.6)	0 (0.0)
≥65	42	18 (42.9)	23 (54.8)	1 (2.4)
Change in opioid medication from visit 2 to 5[b]				
Decrease	1	1 (100.0)	0 (0.0)	0 (0.0)
No change	241	120 (49.8)	117 (48.5)	4 (1.7)
Increase	4	3 (75.0)	1 (25.0)	0 (0.0)

PEG, polyethylene glycol.
[a]The denominator for calculating percentages was the total number of per-protocol patients in each subgroup.
[b]To classify any change in opioid medication, the medication dose at visit 2 was used as the baseline.

(48/123) of patients preferring naloxegol and for 27.4% (32/117) of patients preferring PEG 3350 (Figure 4).

Changes in OIC symptoms based on the BFI and PGIC. Reductions in the BFI score were similar between treatments, with a mean (s.d.) change from baseline to visits 3/5 of −25.0 (31.64) with naloxegol and −26.0 (28.82) with PEG 3350 (95% confidence interval for difference, −4.7 to 3.0; Figure 5a and Table S2 (see Supplementary Digital Content 1, http://links.lww.com/AJG/A169)). Overall, each PGIC response was reported by similar proportions of patients treated with naloxegol or PEG 3350. In the full-analysis set, the mean (s.d.) PGIC score measured at the end of each 2-week treatment period (visits 3 and 5) was 4.5 (1.83) with either naloxegol or PEG 3350 (95% confidence interval for difference, −0.3 to 0.3); the median was anchored at 5.0 ("moderately better, and a slight but noticeable change") with either treatment (Figure 5b and Table S2 (see Supplementary Digital Content 1, http://links.lww.com/AJG/A169)).

When BFI and PGIC scores were analyzed according to patient preference, clinically relevant results supporting reported preference were observed (Figure 5 and Table S3 (see Supplementary Digital Content 1, http://links.lww.com/AJG/A169)). Among patients preferring naloxegol, the mean BFI score reduction after 2 weeks of naloxegol treatment (mean (s.d.), −33.5 (28.49)) was nearly twice the mean BFI score reduction after PEG 3350 (−17.6 (29.00)). Similarly, among patients preferring PEG 3350, the mean (s.d.) BFI score reduction after 2 weeks of treatment was −34.1 (26.09) after PEG 3350 treatment compared with −14.5 (32.21) after naloxegol treatment.

Rescue medication use. Over the 2-week treatment periods, the mean (s.d.) dose of bisacodyl used by patients receiving naloxegol was 2.5 (5.98) mg, and the mean (s.d.) dose used by patients receiving PEG 3350 was 3.9 (9.46) mg. Overall, rescue medication use was lower during both treatment periods compared with the washout periods before treatment (mean (s.d.) dose: naloxegol, 9.5 (18.23) mg; PEG 3350, 10.3 (16.36) mg). The proportion of patients who used rescue medication at least 4 times over 2 weeks was 4.1% (11/267) when receiving naloxegol and 6.7% (18/267) when receiving PEG 3350. Similar proportions of patients did not require rescue therapy when receiving naloxegol (75.7% (202/267)) or PEG 3350 (73.4% (196/267)).

Prespecified subgroup analyses: Factors associated with patient preference

Previous laxative exposure. In a prespecified subgroup analysis examining previous laxative exposure, a numerically higher proportion of patients with laxative use within the 2 weeks before screening preferred naloxegol compared with PEG 3350 (56.0% (47/84) vs 41.7% (35/84)), whereas preference for naloxegol or PEG 3350 was similar among patients without laxative use within the 2 weeks before screening (Table 2).

Age. In an analysis by age, a numerically higher proportion of patients younger than 50 years preferred naloxegol (53.4% (31/58)) compared with PEG 3350 (41.4% (24/58)), whereas a higher proportion of patients aged 65 years or older preferred PEG 3350 (54.8% (23/42)) compared with naloxegol (42.9% (18/42); Table 2).

Previous naloxegol or PEG 3350 use. Among patients who had used naloxegol during the previous year (n = 13), a higher proportion of patients preferred naloxegol compared with PEG 3350; in contrast, among patients who had previously used PEG 3350 (n = 35), the proportions of patients preferring naloxegol or PEG 3350 were comparable (Table 2).

Table 3. TEAEs with an incidence ≥2% in either treatment group (safety-analysis population)

System organ class Preferred term	Naloxegol (n = 271)	PEG 3350 (n = 268)
Gastrointestinal disorders	44 (16.2)	29 (10.8)
Abdominal pain	15 (5.5)	6 (2.2)
Upper abdominal pain	10 (3.7)	4 (1.5)
Diarrhea	11 (4.1)	4 (1.5)
Flatulence	9 (3.3)	9 (3.4)
Nervous system disorders	12 (4.4)	0 (0.0)
Headache	6 (2.2)	0 (0.0)

PEG, polyethylene glycol; TEAE, treatment-emergent adverse event.

Opioid dose. The number of patients with a change (increase or decrease) in their opioid dose was too small to draw any conclusions regarding preferences (Table 2).

Safety

Overall, AEs were reported in 24.4% (66/271) of patients while receiving naloxegol and 17.2% (46/268) of patients while receiving PEG 3350. The most common treatment-emergent AEs reported (incidence ≥2% with either treatment) included abdominal pain, upper abdominal pain, diarrhea, flatulence, and headache (Table 3). One or more serious AEs were reported for 1.1% (3/271) of patients while taking naloxegol and 0.4% (1/268) of patients while taking PEG 3350 (Table S5, see Supplementary Digital Content 1, http://links.lww.com/AJG/A169). Safety profiles were otherwise consistent with the known safety profiles for naloxegol and PEG 3350.

One or more AEs leading to discontinuation of the study drug were reported for 3.3% (9/271) of patients while taking naloxegol and 1.1% (3/268) of patients while taking PEG 3350, and 1 or more AEs leading to study discontinuation were reported for 2.6% (7/271) and 0.7% (2/268) of patients, respectively.

Exploratory outcomes

Diary-reported BMs and stool consistency and straining. Exploratory outcomes reported by patients in a diary are shown for the overall population in Table S4 (see Supplementary Digital Content 1, http://links.lww.com/AJG/A169). Mean stool consistency scores assessed by the BSFS, straining scores, and numbers of BMs and SBMs over 2 weeks of treatment were similar with both naloxegol and PEG 3350.

Post hoc subgroup analyses

Factors associated with patient preference: Age, dose, duration of opioid use, and opioid product use. There were no differences in sex distribution among patients who preferred naloxegol (female, 65.3% (81/124)) and those who preferred PEG 3350 (66.1% (78/118)). The proportions of patients preferring naloxegol or PEG 3350 were comparable for patients on opioid doses of less than 100 MEU and those on opioid doses of 100 MEU or greater (Table S6, see Supplementary Digital Content 1, http://links.lww.com/AJG/A169). Similarly, preference for naloxegol or PEG 3350 was comparable regardless of the duration of opioid use before study entry (Table S6, see Supplementary Digital Content 1, http://links.lww.com/AJG/A169). A numerically higher proportion of patients taking multiple opioid products before study entry expressed a preference for naloxegol compared with PEG 3350 (Table S6, see Supplementary Digital Content 1, http://links.lww.com/AJG/A169).

Factors associated with patient preference: At least a 12-point decrease in the BFI (BFI response). Among patients who were BFI responders with naloxegol and not with PEG 3350, 81.3% (39/48) preferred naloxegol and 18.8% (9/48) preferred PEG 3350. Similarly, among patients who were BFI responders with PEG 3350 and not with naloxegol, 83.1% (49/59) preferred PEG 3350 and 15.3% (9/59) preferred naloxegol. Among patients who were BFI responders with both naloxegol and PEG 3350, 55.9% (57/102) preferred naloxegol and 42.2% (43/102) preferred PEG 3350. Among patients who were BFI nonresponders to either treatment, 51.4% (19/37) preferred naloxegol and 45.9% (17/37) preferred PEG 3350.

DISCUSSION

The current phase 4 study used a randomized, crossover, open-label design and was the first to evaluate patient preference for naloxegol, a prescription treatment indicated for OIC, or PEG 3350, an osmotic OTC laxative. Although similar proportions of patients preferred naloxegol and PEG 3350 in this study, the results indicated a strongly dichotomous distribution of patient preference for either treatment. Few patients had no preference (<2%) or only a slight preference (<15%) for 1 treatment. In general, medication characteristics had a similar influence on treatment preference for naloxegol and PEG 3350; however, the terms "more convenient" and "worked quickly" were reported as having strong influences on preference for a numerically higher proportion of patients who preferred naloxegol than those who preferred PEG 3350. "Tolerated better" was reported as having a similar influence on preference for patients who preferred naloxegol and for those who preferred PEG 3350; this rating aligned with the comparable tolerability profiles of naloxegol and PEG 3350, based on AE reporting.

Naloxegol (9) targets the underlying pathogenic mechanism of OIC and has been shown to be safe and effective for managing this disorder (14,15). Specifically, improvements in constipation symptoms and quality of life have been identified (16). Although analyses of multiple secondary and additional end points revealed no significant differences between naloxegol and PEG 3350 when taken daily for 2 weeks, important differences emerged when results were analyzed according to patient preference, adding critical evidence supporting a meaningfully different experience between these 2 treatments. Improvements in OIC symptoms (change in the BFI) and general health status (PGIC) were greater during the treatment period for the medication that the patient preferred. Thus, the alignment between BFI and PGIC assessments and patient-reported preference reinforces the value of patients' self-reported treatment experience in contributing to clinical decision-making regarding treatment. After only 2 weeks of daily treatment with these products, patients were able to report differences that were shown to correspond to the validated clinical evaluation tools of the BFI and PGIC.

Additional analyses were conducted to identify factors that may improve our ability to prognosticate benefits from naloxegol vs PEG 3350. In this study, younger patients (aged <50 years) generally preferred naloxegol, whereas older patients preferred PEG 3350; this may be related to the occurrence of constipation associated with other factors (e.g., comorbidities, a sedentary lifestyle) (17), which may respond to PEG 3350, among older patients. Results of these analyses suggest that patients who had recently used laxative treatments and patients taking multiple opioid products may be more likely to benefit from naloxegol than from PEG 3350. Further research into as-yet unappreciated patient-related factors may assist in identifying predictors of response to prescription treatments and expand on the trends in patient preference based on age and number of opioids used, as identified in the current study.

This was the first randomized, multicenter, phase 4 study to use the BFI not only as a screening baseline criterion but also as a validated marker of change with treatment. The incorporation of the BFI in this study allowed for a better understanding of the relationship between this clinical assessment of constipation and the patient experience of OIC. *Post hoc* analyses of secondary end points by preference showed that clinically relevant changes in BFI and PGIC scores supported patient-reported preference, validating the clinical utility of the BFI for OIC and consensus recommendations on initiating prescription therapies for OIC (3).

The current trial was also the first study to compare patient preference for a prescription treatment for OIC with an OTC laxative and demonstrate alignment of preference with clinical outcomes. Protocols using preference scales similar to those in the current study have been used in previous OIC studies, as well as studies of other symptomatic conditions (e.g., migraine headaches) (11,12). In a previous study that compared the prescription OIC treatment lubiprostone with the OTC laxative senna, both treatments were associated with improvements in OIC-related symptoms and quality of life, but no significant differences were observed between lubiprostone and the OTC laxative in clinically evaluated measures (18).

Consensus guidelines recommend OTC laxatives, such as PEG 3350, as first-line agents for OIC and suggest that the use of prescription treatments, such as naloxegol, be considered for patients with a BFI score of 30 or greater and an inadequate response to OTC laxatives (3). The current study supported the effectiveness of both options for OIC, with similar proportions of patients reporting a strong preference for either treatment. The overall AE rate was numerically lower with PEG 3350 than with naloxegol; however, this study was not designed to measure statistical differences in AE rates between these 2 groups.

There may be a number of limitations in the current study. Given the open-label design, patient-reported preferences, clinical improvement, and side effects, as well as the use of rescue medication, there may be susceptibility to certain biases. PEG 3350 is a widely available, OTC agent, and there is the potential that patients may have considered it less effective because it was not the newer prescription option. Furthermore, although a subgroup analysis was conducted in patients who had taken PEG 3350 in the year before the study, patients may have tried and failed PEG 3350 more than a year before study entry, and this may have biased their preference. Nevertheless, this study design was intended to approximate a real-world clinical setting, in which patients try multiple different medications, while providing robust effectiveness data captured using a validated tool. Furthermore, the medication attributes that patients rated for level of influence on their preference were based on a prespecified list in the protocol. Thus, although this study indicated that effectiveness is a major factor associated with treatment preference, there may have been other factors contributing to preference that were not examined. Patients' decisions about treatments are multifactorial, and this study was not designed to permit a hierarchical evaluation of all factors involved in patient treatment preferences.

The short 2-week duration of each treatment period in this study was established in part based on the approved on-label use of PEG 3350 (19). Although the relatively short duration of the current study could have impacted the perceived effectiveness of the study drugs and patients' preference for treatment, strong preferences for either naloxegol or PEG 3350 emerged, along with clinically meaningful improvements in OIC symptoms. Furthermore, convenience was shown to have a greater influence on preference for naloxegol compared with PEG 3350. It is possible that convenience may affect compliance and hence effectiveness. Taken together, results of the current study showed a clear strong patient preference for the 2 treatments, and preferences were aligned with clinically meaningful symptom improvements.

In this randomized, crossover, open-label study, patients with OIC reported similar preference rates and strong preferences for daily naloxegol or PEG 3350 treatment, which was generally supported by clinically relevant and measurable improvements in OIC symptoms.

CONFLICTS OF INTEREST

Guarantor of the article: Catherine Datto, MD, MS.
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Study Highlights

WHAT IS KNOWN

- ✓ A common side effect of opioid use in individuals with noncancer pain is constipation.
- ✓ OTC laxatives are recommended as first-line therapy for OIC.
- ✓ Patient preferences for OIC treatment, particularly prescription vs OTC laxatives, are poorly understood.

WHAT IS NEW HERE

- ✓ In this first head-to-head study, patients with noncancer pain reported similar preference rates and strong preferences for naloxegol or PEG 3350.
- ✓ Preference for naloxegol or PEG 3350 was associated with clinical improvements on the BFI and PGIC in patients with OIC.
- ✓ Among patients aged <50 years or receiving laxatives within the previous 2 weeks, a numerically greater proportion preferred naloxegol.

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