Supplementary Material

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

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Supplementary Methods

Study Design

At the initial screening visit (Visit 1), eligible patients entered a 1-week washout period, during which all treatments for OIC were discontinued, and discontinuation of prior treatment for OIC was maintained for the duration of the study. Patients were provided with bisacodyl (up to three 5-mg tablets taken as a single daily dose) to be used as rescue therapy if a bowel movement (BM) had not occurred within 72 hours of the last recorded BM. After the initial washout, eligibility and BFI scores (**Supplementary Figure 1**) were reassessed, and eligible patients were subsequently randomly assigned to receive either naloxegol (25 mg once daily) or PEG 3350 (17 g in 8 ounces of water once daily) for 2 weeks. At the end of the first 2-week treatment period, patients began a second 1-week washout period, during which patients received no interventions for constipation, except bisacodyl as rescue medication to be used as needed. Following the

second 1-week washout period, patients were switched to either naloxegol or PEG 3350 (whichever they did not receive during the first treatment period) for a second 2-week treatment period.

Inclusion and Exclusion Criteria

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 BMs (SBMs) per week, straining (>25% of defecations), sensation of incomplete evacuation (>25% of defecations), lumpy or hard stools (>25% of defecations) (11), and/or sensation of anorectal obstruction/blockage (>25% of defecations). Patients were also required to have a BFI score of 30 or greater prior to the first treatment period (Visits 1 and 2) and to 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.

Patients receiving opioids for the treatment of cancer-related pain and those who had a history of cancer within 5 years (except for successfully treated basal or squamous cell carcinoma of the skin) were excluded. Patients were also excluded if they had constipation unrelated to opioid use, a history of rectal evacuation disorders, the need to perform manual maneuvers to facilitate a BM, or had undergone surgery or procedures that could affect pelvic floor function. Additional GI-related exclusion criteria included: evidence of significant structural abnormalities of the GI tract or diseases/conditions that affect bowel transit; acute or chronic conditions related to the GI tract that could pose a risk to the patient or confound study results (eg, clinically diagnosed diarrhea, fecal incontinence, inflammatory bowel disease); surgery that could affect GI motility

or increase risk for bowel obstruction or perforation within 2 months of Visit 1; and ongoing therapy with medications (other than opioids) that could contribute to constipation. Patients were also excluded from the study based on the following criteria: receiving opioids on a less-than-daily dosing schedule or exhibiting significant withdrawal symptoms; any condition affecting the permeability of the blood-brain barrier; severe background pain refractory to opioids; severe hepatic impairment; creatinine clearance <60 mL/min; pregnant or breastfeeding; currently using methadone, buprenorphine, or other opioid antagonists, concomitant use of strong or moderate cytochrome P450 (CYP) 3A4 inhibitors and strong CYP3A4 inducers; history of intolerance or hypersensitivity to polyethylene glycol (PEG) 3350, naloxegol, bisacodyl, or any of their excipients; active substance or alcohol use that could compromise the ability to comply with study instructions; or received investigational medicine within 30 days of screening.

Statistical Analyses: Sample Size Calculation

Using a 0.050 level chi-squared cutoff, a required sample size of 102 patients in each treatment sequence cohort was calculated to provide 88% power to distinguish between the 2 groups when the proportions in the 3 preference categories (prefer first treatment, no preference, prefer second treatment) were characterized by an effect size of 0.0588. This sample size calculation assumed a 20% difference in preference for treatment 1 over treatment 2 and that 25% of patients would have no preference. Assuming a dropout rate of 20%, randomization of 256 patients was necessary to provide 102 patients per treatment sequence for the primary analysis.

Reference

1. Rentz AM, Yu R, Muller-Lissner S et al. Validation of the Bowel Function Index to detect clinically meaningful changes in opioid-induced constipation. J Med Econ 2009;12:371-83.

Supplementary Table 1. Patient Preference by Treatment Sequence (per-protocol population)

Preference, n (%)	Naloxegol/PEG 3350 (n = 125)	PEG 3350/naloxegol (n = 121)
Preferred naloxegol	62 (49.6)	62 (51.2)
Strong preference for naloxegol	37 (29.6)	38 (31.4)
Moderate preference for naloxegol	14 (11.2)	17 (14.0)
Slight preference for naloxegol	11 (8.8)	7 (5.8)
Preferred PEG 3350	61 (48.8)	57 (47.1)
Strong preference for PEG 3350	9 (7.2)	8 (6.6)
Moderate preference for PEG 3350	15 (12.0)	23 (19.0)
Slight preference for PEG 3350	37 (29.6)	26 (21.5)
No preference	2 (1.6)	2 (1.7)

PEG, polyethylene glycol.

Supplementary Table 2. PGIC at Visits 3/5 and Change in BFI from Baseline to Visits 3/5 (full-analysis population)

End point Randomized sequence	Naloxegol	PEG 3350
Change in BFI from baseline to Visit 3/5		
Overall	*(n = 266)*	*(n = 266)*
Mean (SD)	−25.0 (31.64)	−26.0 (28.82)
Median	−20.0	−23.0
Minimum, maximum	(−98, 93)	(−100, 93)
Naloxegol/PEG 3350	*(n = 132)*	*(n = 129)*
Mean (SD)	−28.8 (29.08)	−23.8 (31.03)
Median	−24.0	−23.0
Minimum, maximum	(−93, 36)	(−100, 93)
PEG 3350/naloxegol	*(n = 134)*	*(n = 137)*
Mean (SD)	−21.3 (33.68)	−28.0 (26.53)
Median	−18.5	−24.0
Minimum, maximum	(−98, 93)	(−88, 22)
PGIC at Visit 3/5		
Overall	*(n = 262)*	*(n = 266)*
Mean (SD)	4.5 (1.83)	4.5 (1.83)
Median	5.0	5.0
Minimum, maximum	(1, 7)	(1, 7)
Naloxegol/PEG 3350	*(n = 132)*	*(n = 129)*
Mean (SD)	4.4 (1.64)	4.5 (1.92)
Median	5.0	5.0
Minimum, maximum	(1, 7)	(1, 7)
PEG 3350/naloxegol	*(n = 130)*	*(n = 137)*
Mean (SD)	4.5 (2.02)	4.4 (1.75)
Median	5.0	5.0
Minimum, maximum	(1, 7)	(1, 7)

BFI, Bowel Function Index; PEG, polyethylene glycol; PGIC, Patient Global Impression of Change; SD, standard deviation.

Supplementary Table 3. BFI Change from Baseline and PGIC by Patient Preference (per-protocol population)

Outcome	Treatment period: naloxegol	Treatment period: PEG 3350
BFI change from baseline (Visit 3/5)		
Preferred naloxegol		
n	124	123
Mean (SD)	−33.5 (28.49)	−17.6 (29.00)
Median	−33.0	−13.0
Minimum, maximum	(−98, 72)	(−86, 93)
Preferred PEG 3350		
n	118	118
Mean (SD)	−14.5 (32.21)	−34.1 (26.09)
Median	−8.5	−30.0
Minimum, maximum	(−93, 93)	(−100, 14)
PGIC at end of each treatment period		
Preferred naloxegol		
n	124	124
Mean (SD)	5.1 (1.66)	4.0 (1.81)
Median	6.0	4.0
Minimum, maximum	(1, 7)	(1, 7)
Preferred PEG 3350		
n	116	117
Mean (SD)	3.9 (1.80)	5.1 (1.58)
Median	4.0	5.0
Minimum, maximum	(1, 7)	(1, 7)

BFI, Bowel Function Index; PEG, polyethylene glycol; PGIC, Patient Global Impression of Change; SD, standard deviation.

Supplementary Table 4. Exploratory Outcomes: Stool Consistency Score by BSFS, Straining Score, and Number of BMs and Spontaneous BMs (per-protocol population)

Outcome over treatment weeks 1 and 2, mean (SD)	Naloxegol (n = 267)	PEG 3350 (n = 267)
Stool consistency score by BSFS	3.9 (1.22)	4.0 (1.16)
Straining score	2.5 (0.89)	2.4 (0.92)
Number of BMs	6.0 (3.35)	5.9 (3.20)
Number of spontaneous BMs	5.9 (3.42)	5.6 (3.28)

BM, bowel movement; BSFS, Bristol Stool Form Scale; PEG, polyethylene glycol; SD, standard deviation.

Supplementary Table 5. Serious AEs Reported During the Study (safety-analysis population)

Serious AE, n (%)	Naloxegol (n = 271)	PEG 3350 (n = 268)	Relationship to study drug
Congestive cardiac failure	1 (0.4)	0 (0.0)	Not related to study drug
Diarrhea	1 (0.4)	0 (0.0)	Reasonable possibility of being caused by the study drug
Gastroenteritis	1 (0.4)	0 (0.0)	Not related to study drug
Salmonellosis	0 (0.0)	1 (0.4)	Not related to study drug
Hypokalemia	1 (0.4)	0 (0.0)	Not related to study drug
Aphasia	1 (0.4)	0 (0.0)	Not related to study drug

AE, adverse event; PEG, polyethylene glycol.

Supplementary Table 6. Patient Preference for Treatment by Subgroups (post hoc analyses; per-protocol population)

Subgroup, n (%)[a]	n	Preferred naloxegol	Preferred PEG 3350	No preference
Opioid dose				
<100 MEU	140	69 (49.3)	68 (48.6)	3 (2.1)
≥100 MEU	106	55 (51.9)	50 (47.2)	1 (0.9)
Opioid duration at baseline				
<1 year	39	15 (38.5)	24 (61.5)	0 (0.0)
1 to 4 years	86	48 (55.8)	37 (43.0)	1 (1.2)
>4 years	120	60 (50.0)	57 (47.5)	3 (2.5)
Opioid product use				
Oxycodone	76	39 (51.3)	36 (47.4)	1 (1.3)
Hydrocodone	43	20 (46.5)	22 (51.2)	1 (2.3)
Morphine	23	12 (52.2)	11 (47.8)	0 (0.0)
Tramadol	17	5 (29.4)	12 (70.6)	0 (0.0)
Fentanyl	2	1 (50.0)	1 (50.0)	0 (0.0)
Oxycocet	2	1 (50.0)	1 (50.0)	0 (0.0)
Codeine	1	0 (0.0)	1 (100.0)	0 (0.0)
Hydromorphone	1	1 (100.0)	0 (0.0)	0 (0.0)
Multiple opioid products used	81	45 (55.6)	34 (42.0)	2 (2.5)

MEU, morphine-equivalent units; PEG, polyethylene glycol.

[a]The denominator for calculating percentages was the total number of per-protocol patients in each subgroup.

Supplementary Figure 1. Bowel function index.[1]

Bowel Function Index (BFI)
1. Ease of defecation (NAS) during the last 7 days according to patient assessment: 0 = easy/no difficulty 100 = severe difficulty 
Ask the subject: "During the last 7 days, how would you rate your ease of defecation on a scale from 0 to 100, where 0 = easy or no difficulty and 100 = severe difficulty?" **If the subject requires clarification, ask:** "During the last 7 days, how easy or difficult was it to have a bowel movement on a scale from 0 to 100, where 0 = easy or no difficulty and 100 = severe difficulty?"
2. Feeling of incomplete bowel evacuation (NAS) during the last 7 days according to patient assessment: 0 = not at all 100 = very strong 
Ask the subject: "During the last 7 days, how would you rate your feeling of incomplete bowel evacuation on a scale from 0 to 100, where 0 = no feeling of incomplete evacuation and 100 = a very strong feeling of incomplete evacuation?" **If the subject requires clarification, ask:** "During the last 7 days, how strongly did you feel that you did not empty your bowels completely? Please indicate how strong this feeling was on a scale from 0 to 100, where 0 = not at all and 100 = very strong"
3. Personal judgement of patient (NAS) regarding constipation during the last 7 days: 0 = not at all 100 = very strong 
Ask the subject: "During the last 7 days, how would you rate your constipation on a scale from 0 to 100, where 0 = not at all and 100 = very strong"

NAS, numerical analogue scale.

 Figure taken from Rentz AM, Yu R, Müller-Lissner S, Leyendecker P. Validation of the Bowel Function Index to detect clinically meaningful changes in opioid-induced constipation, J Med Economics. 2009;12:4, 371-383.