G6

Efficacy of Methylnaltrexone in Patients With Advanced Illness and Opioid-Induced Constipation Refractory to Conventional Laxatives: Impact of Baseline Laxative Use

Gregory S. Sayuk, MD, MPH[1]; Neal E. Slatkin, MD[2,3]; Rowe B. Brookfield, PharmD[3]; Nancy Stambler, DrPH[4]; Robert J. Israel, MD[5]

[1]Washington University School of Medicine, St Louis, MO, USA; [2]University of California Riverside, School of Medicine, Riverside, CA, USA; [3]Salix Pharmaceuticals, Bridgewater, NJ, USA; [4]Progenics Pharmaceuticals, Inc., a subsidiary of Lantheus Holdings, Inc., North Billerica, MA, USA; [5]Bausch Health US, LLC, Bridgewater, NJ, USA

INTRODUCTION

- An estimated 40% to 80% of patients prescribed opioid analgesics for chronic pain experience opioid-induced constipation (OIC) due to opioid stimulation of enteric μ-opioid receptors[1]
- Patients who develop OIC have longer hospital stays, greater hospital costs, and an increased risk of readmission compared with those who do not develop OIC[2,3]
- Although laxatives (eg, stimulants, osmotic agents, and stool softeners) are used to manage OIC, patients often report that they are ineffective and associated with bothersome side effects, such as bloating, urgency, and gas[4]
- Methylnaltrexone (MNTX) is a peripherally acting μ-opioid receptor antagonist
  - MNTX has minimal central nervous system (CNS) penetration; thus, it does not interfere with the analgesic effect of opioids in the CNS, but it blocks opioid actions at μ-opioid receptors in the gastrointestinal (GI) system, providing relief from OIC[5]
  - MNTX is indicated for the treatment of OIC in adults with chronic noncancer pain who do not require frequent (ie, weekly) opioid dosage escalation and in adults with advanced illness or pain caused by active cancer who require opioid dosage escalation for palliative care[6]
- We evaluated whether baseline use of laxatives affects the efficacy and safety of MNTX in patients with chronic pain and OIC

METHODS

Study Design

- This was a post hoc analysis of rescue-free laxation (RFL) responses and treatment-emergent adverse events (TEAEs) with subcutaneous (SC) MNTX versus placebo (PBO) for the treatment of OIC in patients with and without cancer
- Data from 2 multicenter, randomized, double-blind, PBO-controlled, institutional review board–approved clinical studies were pooled for analysis (Figure 1)
  - Study 302 (NCT00402038)[7]
    - Comparison of SC MNTX 0.15 mg/kg (adjustable to 0.30 mg/kg beginning on day 9) with PBO every other day for 14 days
  - Study 4000 (NCT00672477)[8]
    - Comparison of body weight category-based dosing of SC MNTX 8 mg (38 – < 62 kg) or 12 mg (≥ 62 kg) with PBO every other day for 14 days
- Patients were stratified according to baseline laxative regimen
  - Stimulants (eg, senna, bisacodyl)
  - Stool softener (eg, docusate sodium)
  - Osmotic agents (eg, milk of magnesia, polyethylene glycol, lactulose, sorbitol)
  - Stimulants + osmotic agents
  - Stimulants + stool softeners
  - Osmotic agents + stool softeners
  - Stimulants + osmotic agents + stool softeners
  - No laxative use
- The baseline laxative regimen was permitted to continue during both studies

Key Eligibility Criteria

- Aged ≥18 years
- Advanced illness with life expectancy ≥ 1 month
- Received opioids for analgesia for ≥ 2 weeks before study entry
- Stable regimen of opioids and laxatives for ≥ 3 days before study entry
- OIC, defined as < 3 bowel movements during the preceding week and no clinically meaningful laxation within 24 hours before the first dose of study drug or no laxation within 48 hours before the first dose of study drug
- Detailed eligibility criteria for each trial are published[7,8]

Assessments

- Proportion of patients with RFL responses within 4 or 24 hours of ≥ 2 of the first 4 doses
- Median time to RFL response after the first dose
- Incidence of TEAEs

Statistical Analysis

- The intent-to-treat population, defined as patients who received at least 1 dose of study medication, was used for the efficacy analyses
- Comparisons of RFL response rates between treatment groups were performed using chi-square tests
- A log-rank test for time to first laxation censored at 24 hours or time of rescue medication was performed in a pairwise manner to compare the MNTX and PBO groups
- There was no adjustment for multiple comparisons in any of the comparisons
- TEAEs were summarized by patient subgroup

RESULTS

Patients

- The pooled analysis population included 358 patients (MNTX n = 175; PBO n = 183)
- More than 98% of patients in both treatment groups were receiving a laxative regimen at baseline, indicating that OIC in the study population was largely refractory to laxatives
- Baseline laxative use was similar in patients who received MNTX and PBO
  - Stimulants only: MNTX 20.6%; PBO 17.5%
  - Osmotic agents only: MNTX 12.0%; PBO 8.2%
  - Stool softener only: MNTX 6.3%; PBO 7.1%
  - Stimulants + osmotic agents: MNTX 13.1%; PBO 19.7%
  - Stimulants + stool softeners: MNTX 22.9%; PBO 29.5%
  - Osmotic agents + stool softeners: MNTX 2.3%; PBO 2.2%
  - Stimulants + osmotic agents + stool softeners: MNTX 21.1%; PBO 14.8%
  - No laxatives: MNTX 1.7%; PBO 1.1%
- Table 1 summarizes the baseline demographic and clinical characteristics of these groups

Table 1. Baseline Demographics by Baseline Laxative Use

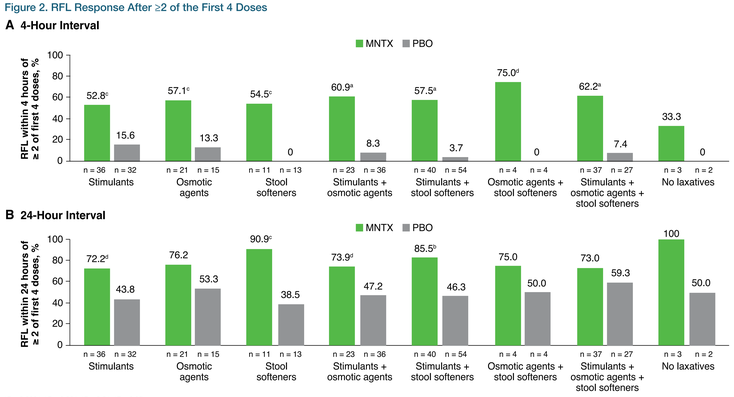
	Stimulants		Osmotic Agents		Stool Softeners		Stimulants + Osmotic Agents		Stimulants + Stool Softeners		Osmotic Agents + Stool Softeners		Stimulants + Osmotic Agents + Stool Softeners		No Laxatives	
	MNTX (n = 36)	PBO (n = 32)	MNTX (n = 21)	PBO (n = 15)	MNTX (n = 11)	PBO (n = 13)	MNTX (n = 23)	PBO (n = 36)	MNTX (n = 40)	PBO (n = 54)	MNTX (n = 4)	PBO (n = 4)	MNTX (n = 37)	PBO (n = 27)	MNTX (n = 3)	PBO (n = 2)
Age, mean (SD), years	65.1 (13.8)	65.6 (14.9)	64.4 (11.7)	60.3 (15.1)	69.2 (15.9)	64.7 (14.0)	66.8 (14.6)	62.6 (12.0)	71.0 (11.7)	70.6 (13.5)	62.5 (10.7)	64.8 (17.6)	63.6 (14.6)	65.9 (12.6)	70.3 (9.7)	83.5 (20.5)
Sex, n (%)																
Male	21 (58.3)	15 (46.9)	11 (52.4)	11 (73.3)	3 (27.3)	6 (46.2)	11 (47.8)	17 (47.2)	22 (55.0)	25 (46.3)	1 (25.0)	1 (25.0)	16 (43.2)	12 (44.4)	1 (33.3)	1 (50.0)
Female	15 (41.7)	17 (53.1)	10 (47.6)	4 (26.7)	8 (72.7)	7 (53.8)	12 (52.2)	19 (52.8)	18 (45.0)	29 (53.7)	3 (75.0)	3 (75.0)	21 (56.8)	15 (55.6)	2 (66.7)	1 (50.0)
Race, n (%)																
Black or African American	1 (2.8)	2 (6.3)	1 (4.8)	0	0	0	0	1 (2.8)	2 (5.0)	2 (3.7)	0	0	1 (2.7)	3 (11.1)	0	0
White	35 (97.2)	29 (90.6)	19 (90.5)	15 (100)	11 (100)	11 (84.6)	22 (95.7)	35 (97.2)	37 (92.5)	52 (96.3)	4 (100)	4 (100)	36 (97.3)	24 (88.9)	2 (66.7)	1 (50.0)
Other	0	1 (3.1)	1 (4.8)	0	0	2 (15.4)	1 (4.3)	0	1 (2.5)	0	0	0	0	0	1 (33.3)	1 (50.0)
ECOG score, n (%)																
0	0	0	0	0	0	0	1 (4.3)	0	1 (2.5)	0	0	0	1 (2.7)	2 (7.4)	0	0
1	8 (22.2)	5 (15.6)	3 (14.3)	2 (13.3)	2 (18.2)	2 (15.4)	3 (13.0)	3 (8.3)	1 (2.5)	5 (9.3)	0	0	3 (8.1)	4 (14.8)	1 (33.3)	0
2	11 (30.6)	8 (25.0)	8 (38.1)	9 (60.0)	3 (27.3)	3 (23.1)	2 (8.7)	11 (30.6)	14 (35.0)	14 (25.9)	2 (50.0)	1 (25.0)	14 (37.8)	9 (33.3)	0	1 (50.0)
3	13 (36.1)	14 (43.8)	8 (38.1)	2 (13.3)	5 (45.5)	7 (53.8)	11 (47.8)	15 (41.7)	18 (45.0)	27 (50.0)	1 (25.0)	2 (50.0)	15 (40.5)	10 (37)	1 (33.3)	0
4	4 (11.1)	5 (15.6)	2 (9.5)	2 (13.3)	1 (9.1)	1 (7.7)	6 (26.1)	7 (19.4)	6 (15.0)	8 (14.8)	1 (25.0)	1 (25.0)	4 (10.8)	2 (7.4)	1 (33.3)	1 (50.0)
Weight, mean (SD), kg	68.9 (12.0)	67.5 (17.2)	73.2 (21.0)	71.1 (20.5)	70.9 (19.4)	78.9 (17.36)	64.3 (15.0)	73.7 (20.0)	75.6 (26.2)	71.8 (32.1)	97.2 (15.0)	76.4 (26.8)	71.3 (17.7)	77.0 (22.1)	58.3 (21.0)	54.6 (9.1)
Daily dose morphine equivalents, mg/d																
Mean (SD)	327.3 (444.6)	188.8 (181.1)	446.3 (676.1)	254.6 (315.8)	60.9 (55.1)	224.8 (226.2)	342.1 (577.7)	686.4 (1719.4)	494.8 (1046.5)	416.6 (1182.3)	298.9 (200.7)	650.8 (946.8)	407.1 (716.8)	193.5 (138.0)	295.7 (368.2)	187.9 (96.0)
Median (range)	168.5 (0.0-2170.0)	108.3 (0.0-700.0)	193.5 (37.5-2640.0)	140.0 (28.0-1290.8)	40.0 (0.0-180.0)	95.0 (10.0-560.0)	155.0 (40.0-2734.0)	192.5 (20.0-10160.0)	129.0 (0.0-4427.0)	90.0 (0.0 - 7228.6)	325.0 (45.0-500.4)	277.5 (18.0-2030.0)	195.0 (0.0-4070.7)	180.0 (20.6-540.0)	107.2 (60.0-720.0)	187.9 (120.0-255.8)
Primary diagnosis, n (%)																
Cancer	28 (77.8)	18 (56.3)	16 (76.2)	10 (66.7)	7 (63.6)	7 (53.8)	14 (60.9)	22 (61.1)	21 (52.5)	30 (55.6)	3 (75.0)	3 (75.0)	23 (62.2)	21 (77.8)	2 (66.7)	1 (50.0)
Cardiovascular disease	2 (5.6)	4 (12.5)	2 (9.5)	1 (6.7)	2 (18.2)	4 (30.8)	1 (4.3)	3 (8.3)	9 (22.5)	5 (9.3)	0	1 (25.0)	5 (13.5)	2 (7.4)	0	0
Neurologic disease	1 (2.8)	2 (6.3)	1 (4.8)	1 (6.7)	1 (9.1)	0	2 (8.7)	2 (5.6)	2 (5.0)	5 (9.3)	0	0	2 (5.4)	0	0	0
Pulmonary disease	5 (13.9)	3 (9.4)	1 (4.8)	0	1 (9.1)	0	3 (13.0)	6 (16.7)	7 (17.5)	6 (11.1)	0	0	6 (16.2)	3 (11.1)	0	0
Other	0	5 (15.6)	1 (4.8)	3 (20.0)	0	2 (15.4)	3 (13.0)	3 (8.3)	1 (2.5)	8 (14.8)	1 (25.0)	0	1 (2.7)	1 (3.7)	1 (33.3)	1 (50.0)

ECOG = Eastern Cooperative Oncology Group; MNTX = methylnaltrexone; PBO = placebo; SD = standard deviation.

Efficacy

- Patients receiving MNTX were more likely than patients receiving PBO to have RFL responses within 4 or 24 hours of ≥2 of the first 4 doses, regardless of baseline laxative regimen (Figure 2)
- For the 4-hour interval, differences were significant ($P < 0.05$) in every subgroup except the no laxatives group
- For the 24-hour interval, differences were significant in the stimulants, stool softeners, stimulants + osmotic agents, and stimulants + stool softeners groups

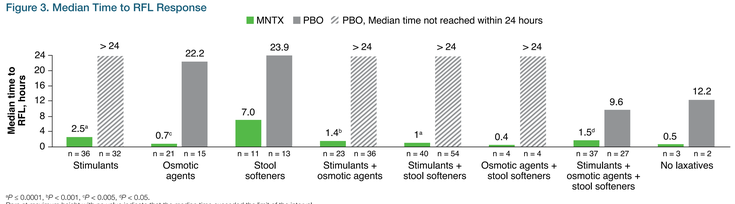
Figure 2. RFL Response After ≥2 of the First 4 Doses



[b]$P < 0.0001$, [c]$P < 0.001$, [d]$P < 0.01$, [a]$P < 0.05$.
MNTX = methylnaltrexone; PBO = placebo; RFL = rescue-free laxation.

- The median time to RFL response was significantly shorter for patients who received MNTX vs PBO across almost all laxative subgroups (Figure 3)
- Median time to RFL ranged from 0.4 to 7.0 hours in the MNTX group
- In the PBO group, median time to RFL response was only reached in patients on osmotic agents, stool softeners, stimulants + osmotic agents + stool softeners, and patients not using laxatives. Median times ranged from 9.6 to 23.9 hours in those groups

Figure 3. Median Time to RFL Response



[a]$P \leq 0.0001$, [b]$P < 0.001$, [c]$P < 0.005$, [d]$P < 0.05$.
Bars at maximum height with no value indicate that the median time exceeded the limit of the interval.
MNTX = methylnaltrexone; PBO = placebo; RFL = rescue-free laxation.

Safety

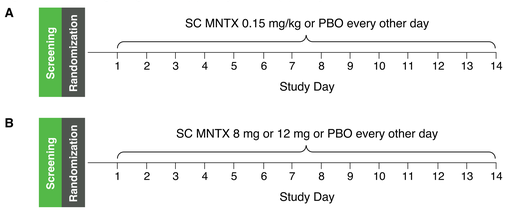
- Overall, most patients reported TEAEs (MNTX, 80.0%; PBO, 69.4%)
- TEAEs were more frequent with MNTX vs PBO in all subgroups except the stimulants + stool softeners and osmotic agents + stool softeners groups (Table 2)
- The most common TEAEs were GI AEs, and no new or unusual safety signals were observed in any subgroup

Table 2. Treatment-Emergent Adverse Events in ≥5% of Patients in Any Group by Baseline Laxative Use

	Stimulants		Osmotic Agents		Stool Softeners		Stimulants + Osmotic Agents		Stimulants + Stool Softeners		Osmotic Agents + Stool Softeners		Stimulants + Osmotic Agents + Stool Softeners		No Laxatives	
TEAE, n (%)	MNTX (n = 37)	PBO (n = 32)	MNTX (n = 21)	PBO (n = 15)	MNTX (n = 11)	PBO (n = 13)	MNTX (n = 23)	PBO (n = 36)	MNTX (n = 40)	PBO (n = 54)	MNTX (n = 4)	PBO (n = 4)	MNTX (n = 37)	PBO (n = 27)	MNTX (n = 3)	PBO (n = 2)
≥ 1 TEAE	32 (86.5)	22 (68.8)	18 (85.7)	9 (60.0)	8 (72.7)	8 (61.5)	20 (87)	25 (69.4)	26 (65)	40 (74.1)	3 (75.0)	3 (75.0)	30 (81.1)	20 (74.1)	3 (100)	0
Abdominal pain	7 (18.9)	0	9 (42.9)	2 (13.3)	0	0	3 (13.0)	5 (13.9)	6 (15.0)	7 (13.0)	1 (25.0)	0	11 (29.7)	5 (18.5)	0	0
Abdominal pain NOS	3 (8.1)	4 (12.5)	1 (4.8)	0	0	2 (15.4)	5 (21.7)	2 (5.6)	1 (2.5)	0	0	0	1 (2.7)	1 (3.7)	0	0
Abdominal pain upper	1 (2.7)	0	0	0	1 (9.1)	0	1 (4.3)	0	0	0	1 (25.0)	0	0	2 (7.4)	0	0
Abdominal discomfort	0	0	0	0	0	0	2 (8.7)	0	0	1 (1.9)	0	0	1 (2.7)	0	0	0
Abdominal distension	0	0	2 (9.5)	0	0	0	1 (4.3)	3 (8.3)	0	3 (5.6)	0	0	2 (5.4)	4 (14.8)	0	0
Abdominal tenderness	0	0	0	0	0	0	1 (4.3)	3 (8.3)	0	0	0	0	0	1 (3.7)	0	0
Malignant neoplasm progression	3 (8.1)	2 (6.3)	0	0	0	1 (7.7)	2 (8.7)	1 (2.8)	0	0	0	0	0	0	0	0
Disease progression	1 (2.7)	1 (3.1)	1 (4.8)	0	0	0	0	1 (2.8)	0	3 (5.6)	0	1 (25.0)	4 (10.8)	1 (3.7)	0	0
Diarrhea	1 (2.7)	2 (6.3)	0	1 (6.7)	0	0	0	2 (5.6)	2 (5.0)	6 (11.1)	2 (50.0)	0	3 (8.1)	4 (14.8)	0	0
Diarrhea NOS	2 (5.4)	1 (3.1)	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Fecaloma	0	2 (6.3)	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Flatulence	1 (2.7)	2 (6.3)	3 (14.3)	1 (6.7)	0	1 (7.7)	4 (17.4)	0	4 (10.0)	4 (7.4)	2 (50.0)	0	2 (5.4)	2 (7.4)	0	0
Nausea	2 (5.4)	2 (6.3)	4 (19.0)	2 (13.3)	0	2 (15.4)	3 (13.0)	5 (13.9)	4 (10.0)	4 (7.4)	2 (50.0)	2 (50.0)	3 (8.1)	3 (11.1)	0	0
Vomiting	0	0	2 (9.5)	0	0	1 (7.7)	1 (4.3)	3 (8.3)	0	2 (3.7)	0	1 (25.0)	1 (2.7)	2 (7.4)	0	0
Vomiting NOS	1 (2.7)	3 (9.4)	0	0	0	1 (7.7)	2 (8.7)	2 (5.6)	3 (7.5)	1 (1.9)	1 (25.0)	0	0	1 (3.7)	0	0
Dehydration	1 (2.7)	1 (3.1)	0	1 (6.7)	0	2 (15.4)	0	0	2 (5.0)	0	0	1 (25.0)	0	0	0	0
Urinary tract infection NOS	1 (2.7)	0	0	0	0	2 (15.4)	0	1 (2.8)	1 (2.5)	0	0	0	0	0	0	0
Pain exacerbated	1 (2.7)	2 (6.3)	0	0	1 (9.1)	2 (15.4)	0	1 (2.8)	0	1 (1.9)	0	0	0	0	0	0
Back pain	1 (2.7)	0	2 (9.5)	0	0	0	3 (13.0)	0	2 (5.0)	2 (3.7)	0	0	3 (8.1)	1 (3.7)	1 (33.3)	0
Headache	1 (2.7)	0	0	0	0	2 (15.4)	1 (4.3)	0	0	1 (1.9)	1 (25.0)	0	1 (2.7)	0	0	0
Body temperature increased	0	0	0	0	3 (27.3)	0	1 (4.3)	0	1 (2.5)	1 (1.9)	0	1 (25.0)	0	0	0	0
Peripheral edema	2 (5.4)	1 (3.1)	0	0	0	1 (7.7)	3 (13.0)	4 (11.1)	3 (7.5)	0	0	1 (25.0)	2 (5.4)	3 (11.1)	0	0
Pyrexia	0	0	0	2 (13.3)	0	0	2 (8.7)	3 (8.3)	2 (5.0)	1 (1.9)	1 (25.0)	0	1 (2.7)	0	0	0
Tachycardia	0	0	0	0	0	0	0	1 (2.8)	0	0	0	0	0	1 (3.7)	0	0
Tachycardia NOS	0	0	0	0	0	2 (15.4)	0	0	1 (2.5)	0	0	0	0	2 (7.4)	0	0
Hypotension	0	0	1 (6.7)	0	0	1 (4.3)	0	0	0	0	0	0	2 (5.4)	1 (3.7)	0	0
Dizziness	2 (5.4)	0	2 (9.5)	0	1 (9.1)	0	3 (13.0)	2 (5.6)	1 (2.5)	3 (5.6)	0	0	0	1 (3.7)	0	0
Tremor	2 (5.4)	0	0	0	0	0	0	1 (2.8)	0	3 (5.6)	0	0	0	0	0	0
Anxiety	0	0	0	1 (6.7)	0	0	0	1 (2.8)	0	0	0	0	2 (5.4)	0	0	0
Confusional state	0	0	1 (4.8)	0	1 (9.1)	1 (7.7)	1 (4.3)	5 (13.9)	3 (7.5)	1 (1.9)	0	0	3 (8.1)	2 (7.4)	0	0
Fall	1 (2.7)	0	1 (4.8)	2 (13.3)	0	0	0	3 (8.3)	3 (7.5)	2 (3.7)	0	0	5 (13.5)	3 (11.1)	0	0
Agitation	1 (2.7)	2 (6.3)	0	0	0	0	0	0	1 (2.5)	1 (1.9)	0	0	1 (2.7)	1 (3.7)	0	0
Bronchitis NOS	2 (5.4)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Dyspnea	0	1 (3.1)	0	0	1 (9.1)	0	0	0	1 (2.5)	3 (5.6)	0	1 (25.0)	1 (2.7)	0	0	0
Rales	0	0	0	2 (13.3)	0	0	1 (4.3)	0	0	0	0	0	0	0	0	0
Ecchymosis	2 (5.4)	1 (3.1)	0	0	0	0	0	0	0	0	0	0	1 (2.7)	1 (3.7)	0	0
Erythema	0	0	0	1 (6.7)	0	1 (7.7)	0	0	0	0	0	0	0	2 (5.4)	0	0
Pruritus	0	0	0	0	0	0	0	0	0	0	0	0	0	3 (8.1)	0	0
Hot flush	0	0	1 (4.8)	0	0	0	1 (4.3)	0	0	0	0	0	0	2 (5.4)	0	0
Blood albumin decreased	0	0	0	0	0	0	0	0	2 (5.0)	2 (3.7)	0	0	0	0	0	0
Anemia	0	0	0	1 (6.7)	0	0	0	0	1 (2.5)	2 (3.7)	0	0	2 (5.4)	0	0	0
Leukocytosis	0	0	0	0	0	0	0	0	1 (2.5)	0	0	0	2 (5.4)	1 (3.7)	0	0
Sweating increased	2 (5.4)	0	0	0	1 (9.1)	1 (7.7)	0	0	0	1 (1.9)	0	1 (25.0)	0	0	0	0

MNTX = methylnaltrexone; NOS = not otherwise specified; PBO = placebo; TEAE = treatment-emergent adverse event.

Figure 1. Study Design Diagrams for (A) Study 302 and (B) Study 4000



MNTX = methylnaltrexone; PBO = placebo; SC = subcutaneous.

CONCLUSIONS

- In patients with advanced illness and OIC refractory to conventional laxatives, treatment with MNTX significantly increased the proportion of patients with RFL, regardless of baseline laxative regimen
- Median time to RFL response was shorter with MNTX vs PBO regardless of baseline laxative regimen
- Consistent with prior reports, GI AEs were the most common TEAEs in all laxative regimen subgroups of patients treated with MNTX

REFERENCES

1. Argoff CE. *Clin J Pain*. 2020;36(9):716-722.
2. Wittbrodt ET, et al. *J Pain Res*. 2018;11:1017-1025.
3. Wan Y, et al. *Am Health Drug Benefits*. 2015;8(2):93-102.
4. Emmanuel A, et al. *Pain Med*. 2017;18(10):1932-1940.
5. Webster LR, Israel RJ. *J Pain Res*. 2018;11:1503-1510.
6. Relistor [package insert]. Bridgewater, NJ: Salix Pharmaceuticals; 2018.
7. Thomas J, et al. *N Engl J Med*. 2008;358(22):2332-2343.
8. Bull J, et al. *J Palliat Med*. 2015;18(7):593-600.

DISCLOSURES

- GS Sayuk is a consultant and speaker for Salix, Ironwood, Allergan, Alnylam, Takeda, GI Health Foundation and Rome Foundation
- NE Slatkin is an employee of Salix Pharmaceuticals, a subsidiary of Bausch Health US
- RB Brookfield is an employee of Salix Pharmaceuticals, a subsidiary of Bausch Health US
- N Stambler is an employee Progenics Pharmaceuticals, Inc., a subsidiary of Lantheus Holdings, Inc
- RJ Israel is an employee of Bausch Health US, LLC

ACKNOWLEDGMENTS

This study was funded by Salix Pharmaceuticals, a division of Bausch Health US, LLC, Bridgewater, NJ, USA, which has licensed the rights to develop and commercialize Relistor® from Progenics Pharmaceuticals, Inc., a wholly owned subsidiary of Lantheus Holdings, Inc., North Billerica, MA, USA. Technical editorial and medical writing assistance was provided under the direction of the authors by Noud van Helmond MD, PhD of Echelon Brand Communications, LLC, an OPEN Health company, Parsippany, NJ, USA. Funding for this assistance was provided by Salix Pharmaceuticals

Research funded by:
Salix Pharmaceuticals