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Repeat Dosing With Subcutaneous Methylnaltrexone: A Pooled Analysis in Patients With and Without Active Cancer

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INTRODUCTION

- Constipation is a common problem in severely and critically ill patients, occurring in a reported 76% to 83% of those admitted to critical care facilities[1-3]
- Opioid use, which is common in these populations,[4] is an important risk factor[1,2,5] and drives constipation through agonism of peripheral μ-opioid receptors throughout the lower gastrointestinal (GI) tract[6-8]
- Conventional laxatives (eg, stimulants, osmotic agents, stool softeners) tend to provide insufficient relief of opioid-induced constipation (OIC),[6-8] likely because these agents do not address the underlying mechanism of OIC
  - Failure to adequately relieve symptoms of OIC can result in reduction or discontinuation of opioid dosing, and consequently suboptimal analgesia[8-10]
- Methylnaltrexone (MNTX; Relistor®, Salix Pharmaceuticals, a division of Bausch Health US, LLC, Bridgewater, NJ, USA) is a selective peripherally acting μ-opioid receptor antagonist that is approved for the treatment of OIC in adult patients with chronic noncancer pain or advanced cancer-related illness who do not require frequent opioid dosage escalation, or patients with pain caused by active cancer who require opioid dosage escalation for palliative care[11]
- Pivotal phase 3 and phase 4 studies have shown MNTX effectively decreases the constipating effect of opioid therapy without attenuating opioid analgesia[12-15]
  - Similar effects have been observed in subpopulations of patients with and without active cancer, with pooled data from 2 pivotal trials in adults with advanced illness and OIC (study 302 [NCT00402038][13]; study 4000 [NCT00672477][15]) showing that more patients achieved rescue-free laxation (RFL) within 4 hours after the first dose of MNTX (cancer, 63.8%; noncancer, 59.7%) compared with placebo (PBO) (cancer, 14.9%; noncancer, 19.7%); regardless of diagnosis
  - Moreover, cumulative benefits have been observed with repeated dosing, with pooled data from the 302 and 4000 studies showing the proportion of patients with an RFL within 4 hours after dosing increased from 62.4% after the first dose of MNTX to 80.9% after the third dose[16]
- The objective of the current analysis was to assess the cumulative efficacy of 7 successive doses of MNTX compared with PBO in patients with active cancer and in patients without a cancer diagnosis[17]

METHODS

- This was a post hoc analysis of pooled data from the similarly designed, multicenter, double-blind, randomized, PBO-controlled 302[13] and 4000[15] studies (Figure 1)

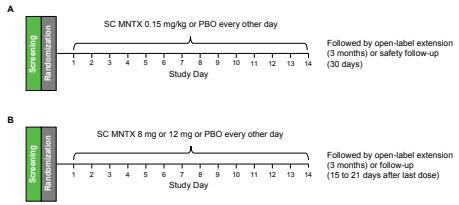
Patients

- Men and women aged ≥18 years with OIC and a diagnosis of advanced medical illness with a life expectancy ≥1 month were eligible to participate
  - OIC: <3 bowel movements during the previous week and no clinically significant laxation during the 24 hours preceding the first dose of study drug or no clinically significant laxation within 48 hours prior to first dose of study drug
  - Advanced medical illness: terminal illness such as incurable cancer or other end-stage disease with a life expectancy of ≥1 month
- Key inclusion criteria:
  - Received chronic opioid therapy for ≥2 weeks prior to baseline, with no dose reduction ≥50% within 3 days prior to study drug initiation
  - Patients using conventional laxatives (eg, stool softeners plus senna or equivalent) were required to be on a stable regimen for ≥3 days prior to study drug initiation
- Key exclusion criteria:
  - Prior MNTX treatment (study 302) or prior MNTX treatment within 7 days of the study dose (study 4000)
  - Possible GI obstruction/fecal impaction
  - Possible nonopioid cause of bowel dysfunction contributing to constipation that, in the opinion of the investigator, was the primary cause of the constipation

Study Design

- Study 302: Patients received subcutaneous (SC) injections of MNTX 0.15 mg/kg or PBO every other day for 14 days (Figure 1A)
  - Dose escalation to 0.30 mg/kg was permitted on day 9 for patients who had <3 bowel movements not associated with rescue medication
- Study 4000: Patients received SC injections of MNTX or PBO every other day for 14 days (Figure 1B)
  - Patients weighing ≥38 to <62 kg received SC MNTX 8 mg or PBO; those weighing ≥62 kg received SC MNTX 12 mg or PBO
- Patients were permitted to continue use of baseline laxatives throughout either study, except within 4 hours after the study dose

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



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

Assessments

- The proportions of patients with ≥1, ≥2, ≥3, ≥4, ≥5, ≥6, and 7 RFLs were examined by treatment group in patients with and without cancer who received all 7 doses of study drug
  - Treatment-group comparisons were based on the Fisher Exact test
- Treatment-emergent adverse events (TEAEs) were described for all patients who received ≥1 dose of study drug in the cancer and noncancer populations using summary statistics

Results

Patients and Disposition

- The pooled study population included 364 patients (PBO = 185, MNTX = 179) who took ≥1 dose of study drug
- Approximately two thirds of patients had a primary diagnosis of active cancer (PBO = 114, MNTX = 116), while the remaining patients had other advanced diseases (PBO = 71, MNTX = 63); additional baseline demographic and clinical characteristics for the cancer and noncancer populations are summarized in Table 1
  - In general, patients with cancer tended to be younger (median age: 63 years vs 71 in noncancer patients) and were more likely to be male (53% vs 41% in noncancer patients)
  - Patients in the cancer population were also receiving nearly twice the dose of opioids at baseline (median morphine equivalent dose: 184 mg) than those with noncancer diagnoses (90 mg)
  - More than 98% of patients across study populations and treatment groups were receiving 1 or more laxatives at baseline
- Overall, 153 patients (66.5%) in the cancer population and 96 patients (72.1%) in the noncancer population received all 7 doses of study drug (Figure 2)

Efficacy

- Cumulative response rates were significantly greater with MNTX than PBO after repeated dosing in both cancer ($P < 0.001$ for all comparisons) and noncancer ($P < 0.01$ for all comparisons) patients who completed all 7 doses (Figure 2)
  - The majority of patients treated with MNTX had ≥1 RFL over 7 doses (cancer, 88.5%; noncancer, 93.2%) compared with just over half of those in the PBO group (cancer, 54.7%; noncancer, 55.8%)
  - Approximately half of patients receiving MNTX achieved ≥4 RFL responses over the course of 7 doses (cancer, 50.0%; noncancer, 54.5%), compared with less than 4% of PBO-treated patients (cancer, 2.7%; noncancer, 3.8%)

Safety

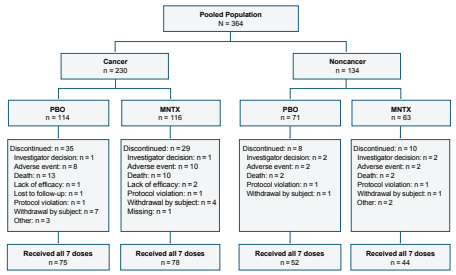
- The most common TEAEs were GI in nature and included abdominal pain, nausea, and flatulence (Table 3)
- Rates of TEAE were generally higher in patients with cancer compared with patients without cancer

Table 1. Study Population Demographics and Baseline Clinical Characteristics: Cancer and Noncancer Groups (ITT Population)

	Cancer (n = 230)		Noncancer (n = 133)	
	PBO (n = 114)	MNTX (n = 116)	PBO (n = 71)	MNTX (n = 62)[a]
Age, median (range), years	64 (32 – 90)	62 (27 – 91)	70 (40 – 98)	73 (34 – 101)
Gender, n (%)				
Male	60 (52.6)	62 (53.4)	29 (40.8)	25 (40.3)
Female	54 (47.4)	54 (46.6)	42 (59.2)	37 (59.7)
Race, n (%)				
White	105 (92.1)	109 (94.0)	68 (95.8)	59 (95.2)
Black or African American	6 (5.3)	4 (3.4)	2 (2.8)	2 (3.2)
American Indian/Alaskan native	0	0	1 (1.4)	1 (1.6)
Asian	0	1 (0.9)	0	0
Other	3 (2.6)	2 (1.7)	0	0
Body weight, mean (SD), kg	71.1 (16.5)	70.9 (16.4)	74.9 (32.7)	71.8 (24.8)
Daily opioid dose morphine equivalents, median (range), mg/day	187.9 (0 – 10,160)	180.0 (0 – 4160)	80 (0 – 663)	120 (0 – 4427)
Primary diagnosis, n (%)				
Cancer	114 (100)	116 (100)	0	0
Cardiovascular disease	0	0	20 (28.2)	21 (33.9)
Pulmonary disease (nonmalignant)	0	0	18 (25.4)	23 (37.1)
Neurologic disease	0	0	10 (14.1)	10 (16.1)
Other	0	0	23 (32.4)	8 (12.9)
Number of laxatives used, n (%)				
0	1 (0.9)	2 (1.7)	1 (1.4)	1 (1.6)
1	31 (27.2)	40 (34.5)	17 (23.9)	16 (25.8)
2	40 (35.1)	40 (34.5)	29 (40.8)	25 (40.3)
3	23 (20.2)	17 (14.7)	17 (23.9)	10 (16.1)
4	14 (12.3)	14 (12.1)	4 (5.6)	4 (6.5)
≥5	5 (4.4)	3 (2.6)	3 (4.2)	6 (9.7)

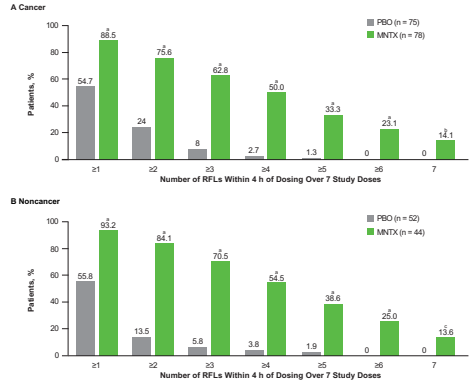
[a]One female patient from study 302 was excluded from this table and the efficacy analyses (but not the TEAE summary statistics) because she received MNTX before being randomized to the MNTX group.
MNTX = methylnaltrexone; PBO = placebo; SD = standard deviation.

Figure 2. Patient Disposition: Cancer and Noncancer Groups



MNTX = methylnaltrexone; PBO = placebo; SD = standard deviation.

Figure 3. Proportion of Patients Treated With MNTX or PBO With Cumulative RFL Within 4 Hours After a Study Dose Over 7 Doses, (A) Cancer and (B) Noncancer Groups (ITT Population)



[a]$P < 0.0001$ vs PBO; [b]$P < 0.001$ vs PBO; [c]$P < 0.01$ vs PBO.
ITT = intent to treat; MNTX = methylnaltrexone; PBO = placebo; RFL = rescue-free laxation.

Table 2. TEAEs Reported in >5% of Patients in Any Treatment Group (Safety Population)

	Cancer		Noncancer	
System Organ Class Preferred Term, n (%)	PBO (n = 114)	MNTX (n = 116)	PBO (n = 71)	MNTX (n = 63)
Patients with ≥1 TEAE	91 (79.8)	102 (87.9)	50 (70.4)	44 (69.8)
Abdominal pain	11 (9.6)	28 (24.1)	8 (11.3)	11 (17.5)
Nausea	16 (14.0)	17 (14.7)	7 (9.9)	3 (4.8)
Flatulence	6 (5.3)	12 (10.3)	4 (5.6)	4 (6.3)
Disease progression	16 (14.0)	10 (8.6)	1 (1.4)	0
Back pain	3 (2.6)	10 (8.6)	0	2 (3.2)
Confusional state	9 (7.9)	9 (7.8)	2 (2.8)	0
Edema peripheral	8 (7.0)	9 (7.8)	4 (5.6)	3 (4.8)
Abdominal pain NOS	6 (5.3)	9 (7.8)	3 (4.2)	2 (3.2)
Fall	8 (7.0)	7 (6.0)	3 (4.2)	3 (4.8)
Vomiting NOS	7 (6.1)	7 (6.0)	2 (2.8)	1 (1.6)
Pyrexia	3 (2.6)	7 (6.0)	4 (5.6)	1 (1.6)
Dizziness	3 (2.6)	7 (6.0)	4 (5.6)	2 (3.2)
Malignant neoplasm progression	13 (11.4)	6 (5.2)	0	1 (1.6)
Diarrhea	9 (7.9)	6 (5.2)	6 (8.5)	3 (4.8)
Vomiting	8 (7.0)	5 (4.3)	2 (2.8)	0
Asthenia	8 (7.0)	4 (3.4)	2 (2.8)	3 (4.8)
Abdominal distension	7 (6.1)	4 (3.4)	4 (5.6)	2 (3.2)
Dehydration	6 (5.3)	3 (2.6)	2 (2.8)	0
Pain exacerbated	6 (5.3)	2 (1.7)	1 (1.4)	0

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

CONCLUSIONS

- In this pooled analysis of severely ill patients with OIC refractory to laxative treatment, MNTX significantly increased the proportion of patients achieving RFL compared with placebo over 7 successive doses in both active cancer and noncancer groups
- Patients with and without active cancer who received MNTX showed persistent and successive RFL responses within 4 hours after administration with repeat dosing, indicating that MNTX effectively treated OIC in both patient populations
- MNTX was generally well tolerated in patients with and without active cancer; for both groups, the most common side effects were consistent with restored laxation
- Repeat dosing of SC MNTX is an effective treatment for OIC that can be safely administered to critically ill patients, including those with active cancer or noncancer illness

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DISCLOSURES

Dr. Shah has nothing to disclose. Dr. Yu has nothing to disclose. Dr. Slatkin is an employee of Salix Pharmaceuticals, a subsidiary of Bausch Health US. Dr. Stambler is an employee of Progenics Pharmaceuticals, Inc., a wholly owned subsidiary of Lantheus Holdings, Inc. Dr. Israel is an employee of Bausch Health US, LLC.

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