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Impact of Subgroups on Methylnaltrexone Efficacy/Safety in Advanced Illness

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INTRODUCTION

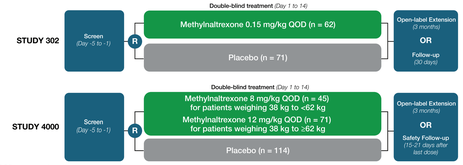
- Opioid-induced constipation (OIC) is a condition associated with abdominal discomfort and pain and is a leading adverse event of opioid use[1,2]
- OIC is believed to occur as a result of opioid binding to peripheral μ-opioid receptors in the gastrointestinal (GI) tract, leading to abnormal modulation of GI secretion and absorption[3]
- Peripheral μ-opioid receptor antagonists (PAMORAs) are indicated for the treatment of OIC
  - PAMORAs have limited ability to cross the blood-brain barrier, thereby reversing μ-opioid binding in the gut without compromising the effects of opioid analgesia[3]
- Methylnaltrexone (MNTX; Relistor®, Salix Pharmaceuticals, a division of Bausch Health US, LLC, Bridgewater, NJ, USA) is a PAMORA approved by the US Food and Drug Administration for the treatment of OIC in adults with chronic noncancer pain, including patients with chronic pain related to previous cancer or its treatment who do not require frequent (eg, weekly) opioid dosage escalation, and for the treatment of OIC in adults with advanced illness or pain caused by active cancer who require opioid dosage escalation for palliative care[4]
- Pivotal clinical trials demonstrated superior efficacy of MNTX over placebo (PBO) in achieving rescue-free laxation (RFL) responses within 4 and 24 hours after the first dose
- Using pooled data from 2 placebo-controlled MNTX trials, this post hoc analysis assessed the impact of baseline patient characteristics on the safety and efficacy of MNTX in those with advanced illness and OIC

METHODS

Study Design

- This post hoc analysis pooled data from 2 randomized, double-blind, PBO-controlled studies of MNTX, including the phase 3 302 [NCT00402038] study and the phase 4 4000 study [NCT00672477][5,6] (**Figure 1**)
  - Study 302 included 133 patients randomized in a 1:1 ratio to receive subcutaneous injections of MNTX 0.15 mg/kg or PBO every other day (QOD) for 14 days, with the opportunity to increase the dose to 0.30 mg/kg on day 9 in patients with <3 RFLs at the investigator's discretion[5]
    - After completion of the double-blind treatment period, patients could enroll in the 3-month open-label extension phase, in which they could receive MNTX as needed up to every 24 hours[5]
  - Study 4000 included patients randomized in a 1:1 ratio to receive subcutaneous MNTX 8 mg or 12 mg for patients weighing 38 kg to 62 kg or ≥62 kg, respectively, or PBO, administered QOD for a maximum of 7 doses/14 days, with the option to enroll in a 10-week open-label extension portion[6]

Figure 1. Study Design[5,6]



QOD = every other day.

Patients

Key Inclusion Criteria

- Aged ≥18 years
- Diagnosis of advanced illness (ie, terminal illness such as incurable cancer, end-stage diseases) with a life expectancy of ≥1 month
- Receiving opioids routinely for discomfort or pain management for ≥2 weeks (excluding as-needed or rescue doses) and taking a stable (ie, <50% reduction in dose) regimen for at least 3 days before the first dose
- OIC defined as either of the following:
  - <3 bowel movements during the previous week and no clinically significant laxation in the 24 hours before first dose of study drug
  - No clinically significant laxation within 48 hours before first dose of study drug
- Receiving stable laxative regimen (eg, stool softener and senna or equivalent) for ≥3 days prior to first dose of study drug

Key Exclusion Criteria

- History of MNTX treatment
- Any disease process suggestive of mechanical bowel obstruction
- Evidence of fecal impaction
- Any potential nonopioid cause of bowel dysfunction, in the opinion of the investigator
- History of fecal ostomy

Study Assessments

- The proportion of patients achieving RFL within 4 or 24 hours after the first dose of study drug was assessed in patient subgroups stratified by baseline age (<65 vs ≥65), cancer status, Eastern Cooperative Oncology Group (ECOG) status (≤2 vs >2), opioid requirement (oral morphine equivalent dose <80 mg/d, 80 to <150 mg/d, and ≥150 mg/d) and laxative type (osmotic agents, stimulants, stool softeners)
- Treatment-emergent adverse events (TEAEs), GI TEAEs, and abdominal pain were evaluated in the pooled population and patient subgroups, stratified by ECOG status, cancer status, laxative type, and opioid requirement

Statistical Analysis

- Efficacy analyses were performed on the intention-to-treat population, defined as patients who received ≥1 dose of study medication
  - Response rates for patients achieving RFL within 4 and 24 hours were compared across treatment groups using the Cochran-Mantel-Haenszel test, and *P* values based on chi-squared tests were generated
  - Nominal levels of significance were set at $P < 0.05$, with no adjustments for multiplicity
- Safety analyses were performed on the safety population, defined as patients who received ≥1 dose of study medication
  - TEAEs were described for each treatment group using summary statistics

RESULTS

Baseline Characteristics

- A total of 363 patients received ≥1 dose of study medication (MNTX, n = 178; PBO, n = 185) across studies and were included in the pooled analyses
- Overall, patients had a mean age of 66 years, and approximately two-thirds of the patients had a cancer diagnosis; the majority of patients had an ECOG score ≥2
- The mean oral morphine equivalent dose was 374.53 mg/d, and almost all patients were taking ≥1 laxative at baseline
- Demographic and clinical characteristics were similar between the MNTX and PBO groups (**Table 1**)

Table 1. Patient Demographics and Baseline Characteristics

	PBO (n = 185)	MNTX (n = 178)	Total (N = 363)
Age, mean (SD), years	66.1 (13.9)	66.5 (13.4)	66.3 (13.7)
Age category, n (%)			
<65 years	89	83	172
≥65 years	96	95	191
Sex, n (%)			
Male	89 (48.1)	87 (48.9)	176 (48.5)
Female	96 (51.9)	91 (51.1)	187 (51.5)
Race, n (%)			
American Indian or Alaskan Native	1 (0.5)	1 (0.6)	2 (0.6)
Asian	0	1 (0.6)	1 (0.3)
Black or African American	8 (4.3)	6 (3.4)	14 (3.9)
White	173 (93.5)	168 (94.4)	341 (93.9)
Other	3 (1.6)	2 (1.1)	5 (1.4)
Ethnicity, n (%)			
Hispanic or Latino	11 (5.9)	11 (6.2)	22 (6.1)
Not Hispanic or Latino	174 (94.1)	167 (93.8)	341 (93.9)
Weight, mean (SD), kg	72.6 (24.0)	71.2 (19.7)	71.9 (22.0)
Primary diagnosis, n (%)			
Cancer	114 (61.6)	116 (65.2)	230 (63.4)
Cardiovascular disease	20 (10.8)	21 (11.8)	41 (11.3)
Neurologic disease	10 (5.4)	10 (5.6)	20 (5.5)
Pulmonary disease	18 (9.7)	23 (12.9)	41 (11.3)
Other	23 (12.4)	8 (4.5)	31 (8.5)
ECOG Score, n (%)			
0	2 (1.1)	3 (1.7)	5 (1.4)
1	21 (11.4)	21 (11.8)	42 (11.6)
2	57 (30.8)	54 (30.3)	111 (30.6)
3	78 (42.2)	73 (41.0)	151 (41.6)
4	27 (14.6)	27 (15.2)	54 (14.9)
OED, mg morphine sulfate/d			
Mean (SD)	372.8 (1016.9)	376.3 (699.9)	374.5 (874.7)
Median (range)	130 (0–10160)	156 (0–4427)	146 (0–10160)
OED categories, n (%)			
<80 mg/day	57	42	99
80 to <150 mg/day	42	39	81
≥150 mg/day	86	97	183
Laxatives used at baseline, n (%)			
Number of laxatives			
0	2 (1.1)	3 (1.7)	5 (1.4)
1	48 (25.9)	56 (31.5)	104 (28.7)
2	69 (37.3)	65 (36.5)	134 (36.9)
3	40 (21.6)	27 (15.2)	67 (18.5)
≥4	26 (14.1)	27 (15.2)	53 (14.6)
Type of laxative[a]			
Osmotic agent	82	85	167
Stimulant	149	136	285
Stool softener	98	92	190

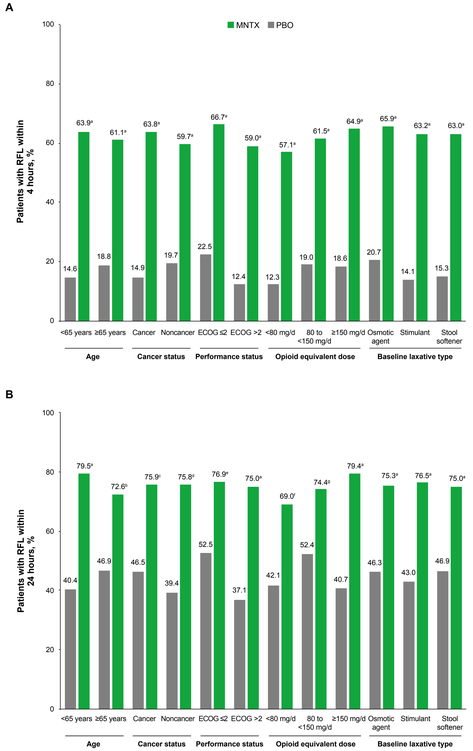
[a]Patients could receive more than one laxative type.

ECOG = Eastern Cooperative Oncology Group; MNTX = methylnaltrexone; OED = opioid equivalent dose; PBO = placebo; SD = standard deviation.

Laxation Response

- A significantly greater proportion of patients receiving MNTX achieved RFL within 4 hours and 24 hours of the first dose vs PBO, regardless of baseline age, cancer status, ECOG performance status, opioid requirement, and laxative type (**Figure 2**)

Figure 2. Rescue-Free Laxation Within 4 Hours After the First Dose (A) and Within 24 Hours After the First Dose (B)



[a]$P < 0.0001$; [b]$P = 0.0003$; [c]$P < 0.005$; [d]$P < 0.05$; [e]$P = 0.0013$; [f]$P = 0.0079$; [g]$P = 0.0407$.

ECOG = Eastern Cooperative Oncology Group; MNTX = methylnaltrexone; PBO = placebo; RFL = rescue-free laxation.

Safety

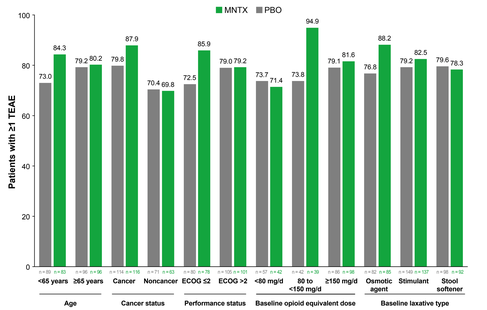
- Most patients experienced ≥1 TEAE in the overall population (MNTX 82.1%; PBO 76.2%); results were similar when stratified by baseline cancer status, ECOG performance status, opioid requirement, and laxative type (**Table 2**)
- The overall incidence of TEAEs was similar between MNTX and placebo and generally similar across baseline characteristics (**Figure 3**)
- The most common TEAEs were GI in nature, and were reported in approximately half of patients receiving MNTX or PBO across subgroups (**Figure 4**)
- Abdominal pain was more common in patients receiving MNTX than PBO across subgroups (**Figure 5**)
  - Abdominal pain associated with MNTX is typically mild to moderate in severity and associated with a laxation response to treatment. Incidence of abdominal pain usually reduces with subsequent MNTX dosing[7]

Table 2. Treatment-Emergent Adverse Events Occurring in ≥5% of Patients in Either Treatment Group

	PBO (n = 185)	MNTX (n = 179)
Patients with ≥1 AE	141 (76.2)	147 (82.1)
Abdominal pain	19 (10.3)	39 (21.8)
Nausea	23 (12.4)	20 (11.2)
Flatulence	10 (5.4)	16 (8.9)
Back pain	3 (1.6)	12 (6.7)
Peripheral edema	12 (6.5)	12 (6.7)
Abdominal pain NOS	9 (4.9)	11 (6.1)
Disease progression	17 (9.2)	10 (5.6)
Fall	11 (5.9)	10 (5.6)
Diarrhea	15 (8.1)	9 (5.0)
Confusional state	11 (5.9)	9 (5.0)
Asthenia	10 (5.4)	7 (3.9)
Malignant neoplasm progression	13 (7.0)	7 (3.9)
Abdominal distension	11 (5.9)	6 (3.4)
Vomiting	10 (5.4)	5 (2.8)

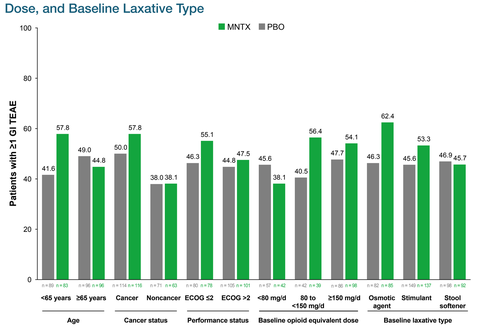
AE = adverse event; MNTX = methylnaltrexone; NOS = not otherwise specified; PBO = placebo.

Figure 3. Overall Incidence of TEAEs in the Pooled Population and Patient Subgroups Stratified by Age, Cancer Status, ECOG Performance Score, Baseline Oral Morphine Equivalent Dose, and Baseline Laxative Type



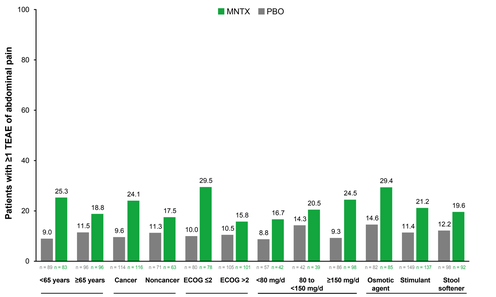
AE = adverse event; ECOG = Eastern Cooperative Oncology Group; MNTX = methylnaltrexone; OED = opioid equivalent dose; PBO = placebo.

Figure 4. Incidence of GI TEAEs Across Patient Subgroups Stratified by Age, Cancer Status, ECOG Performance Score, Baseline Oral Morphine Equivalent Dose, and Baseline Laxative Type



AE = adverse event; ECOG = Eastern Cooperative Oncology Group; GI = gastrointestinal; MNTX, methylnaltrexone; PBO = placebo; TEAEs = treatment-emergent adverse events.

Figure 5. Incidence of Abdominal Pain Across Patient Subgroups Stratified by Age, Cancer Status, ECOG Performance Score, Baseline Oral Morphine Equivalent Dose, and Baseline Laxative Type



AE = adverse event; ECOG = Eastern Cooperative Oncology Group; MNTX = methylnaltrexone; OED = opioid equivalent dose; PBO = placebo.

CONCLUSIONS

- **MNTX treatment was superior to PBO in achieving RFL within 4 and 24 hours of the first dose, regardless of patients' cancer status, baseline ECOG performance status, or baseline opioid or laxative use**
- **MNTX remained consistently safe across different baseline clinical and demographic characteristics**
- **These findings demonstrate that MNTX provides effective and safe relief of OIC in patients with advanced illness regardless of baseline demographic or clinical characteristics, supporting MNTX as a valuable treatment in patients with OIC**

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DISCLOSURES

N Mehta has participated in several advisory boards for Salix Pharmaceuticals. ED Shah has nothing to disclose. RJ Israel is an employee of Bausch Health US, LLC. N Stambler is a full-time employee of Progenics Pharmaceuticals, Inc., a subsidiary of Lantheus Holdings, Inc., and shareholder of Lantheus Holdings, Inc.

ACKNOWLEDGMENTS

The 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, 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 Drayton Hammond, PharmD, 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